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(54) **Cyclopropanone derivatives.**

(57) A novel cyclopropanone derivative (I) which possesses a potent inhibitory activity against thiol protease such as papain, cathepsin B, cathepsin H, cathepsin L, calpain or the like with excellent properties regarding oral absorbance, tissue transference and cell membrane permeability, and are clinically useful in the treatment of various diseases such as muscular dystrophy, amyotrophy. Also provided are a process for producing the compound (I) and a pharmaceutical composition containing the same.

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FIELD OF THE INVENTION

The present invention relates to novel cyclopropanone derivatives. More particularly, this invention relates to novel cyclopropanone derivatives having a potent inhibitory activity against thiol protease such as papain, cathepsin B, cathepsin H, cathepsin L, calpain or the like.

BACKGROUND OF THE INVENTION

In accordance with the elucidation of the *in vivo* activity of thiol protease such as papain, cathepsin B, cathepsin H, cathepsin L, calpain or the like, it has been found that their extraordinary hypersthenia causes various diseases. Further, there is increasing the report which shows thiol protease inhibitors are effective on such disease in animal models.

It is considered that thiol protease such as calpain, cathepsin B or the like take part in the initial process such as disappearance of Z line through the decomposition of muscular fiber protein in the collapse of skeletal muscle as seen in muscular disease such as muscular Dystrophy, amyotrophy or the like [Taisha (Metabolism), 25, 183 (1988)]. Furthermore, E-64-d, namely a thiol protease inhibitor, has been reported to have life-prolonging effect in experimental muscular dystrophy hamster [Journal of Pharmacobio dynamics, 10, 678 (1987)]. Accordingly, such thiol protease inhibitors are expected to be useful as therapeutic agents for the treatment of muscular dystrophy, amyotrophy or the like.

The main cause of the post-ischemic cellular disorder occurs during ischemic diseases such as cardiac infarction, stroke and the like is active oxygen produced by xanthine oxidase. It has been reported that, during the ischemia, the increase in Ca^{2+} concentration results in the activation of calpain which restrictively degrade xanthine dehydrogenase, a precursor of xanthine oxidase, to give xanthine oxidase [New England Journal of Medicine, 312, p.159, (1985)]. It has also been reported that the activation of calpain may directly cause the necrosis of myocardial cells or neurocytes [Saishin Igaku, 43, p.783, (1988)]. There have been reported that NCO-700, a calpain inhibitor, is effective on cardiac infarction when tested on animal models [Arzneimittel Forschung/Drug Research, 36, p.190, p.671, (1986)], and that E-64-C inhibits the degradation of microtubule-associated protein after the brain ischemia [Brain Research, 526, p.177, (1990)]. These reports indicate that a calpain inhibitor can be useful for the treatment of ischemic diseases such as cardiac infarction, stroke and the like.

The cause of senile plaque which is found specifically in the brain of patients suffering from Alzheimer's disease is known to be the precipitated amyloid, a protein produced by the decomposition of an amyloid precursor protein (APP). Although APP does not give amyloid as a normal metabolite, it may be converted into amyloid under an abnormal metabolism where protease is extremely activated, and precipitated as senile plaque [Scientific American, (11), p.40, (1991)]. Therefore, protease inhibitor is expected to be useful for the treatment of Alzheimer's disease.

The activation of calpain has been observed in a brain trauma model of rabbit [Neurochemical Research, 16, p.483, (1991)]. It has also been observed, the administration of leupeptin, a calpain inhibitor, can protect axon in brain trauma models of rat [Journal of Neurosurgery, 65, p.92, (1986)]. Thus, calpain inhibitors are considered to be useful for improving the conscious disturbance or motor disturbance caused by brain trauma.

It has also been reported that myelin-associated protein exists in dendrite of neurocytes is decomposed by calpain [Journal of Neurochemistry, 47, p.1007, (1986)], indicating that calpain inhibitors may be effective on diseases caused by the demyelination of neurocytes such as multiple sclerosis, peripheral nervous neuropathy and the like.

The main cause of the turbidity during cataract is hydrolytic products of a water-soluble protein crystallin by protease in lens. It has been observed the increase in calcium concentration in lens of cataractous animal models and some of human cataract [Investigative Ophthalmology & Visual Science, 28, p.1702, (1987); Experimental Eye Research, 34, p.413, (1982)]. The dominant protease contained in lens is calpain [Lens and Eye Toxicity Research, 6, p.725, (1989)]. These facts indicate that the abnormal sthenia of calpain can be one of the causes of cataract. There is a report that E-64, an inhibitor of calpain, is effective on cataract in animal models [Investigative Ophthalmology & Visual Science, 32, p.533, (1991)], indicating that calpain inhibitors can be useful in the treatment of cataract.

Neutrophils, which is deeply associated to inflammation, show the degranulation or production of superoxides in response to the stimulations by a chemotactic factor or phorbol ester through a mechanism appeared to be mediated by protein kinase C (PKC). Calpain participates in the activation of PKC in the manner where it promotes the degranulation and inhibits the production of superoxides [Journal of Biological Chemistry, 263, p.1915, (1988)]. In another report, the concentration of cathepsin B in macro-

phage in rat is 30 to 40 times that of leukocytes and neutrophils, and the concentration of the enzyme in inflammatory macrophage is 6 times that of normal macrophages [Journal of Biochemistry, 98, p.87, (1985)]. These facts indicate that thiol protease inhibitors are useful as anti-inflammatory drugs.

The type I allergy reaction is mediated by immunoglobulin E (IgE) produced in the subject immunized with an antigen. Estatin A, a thiol protease inhibitor, has been reported to specifically inhibit the production of IgE without affecting on the production of IgG [The Journal of Antibiotics, 42, p.1362, (1989)]. Accordingly, thiol protease inhibitors are considered to be useful as antiallergic drugs.

In case of necrosis of hepatic cells, it is believed that impairment of the cell membrane leads to an increase in the permeability of Ca^{2+} , an increase in intracellular Ca^{2+} concentration, an activation of calpain, and, as the result, the decomposition of its substrate such as skeletal protein takes place, which results in the death of cells. Accordingly, a calpain inhibitor can be used as a therapeutic agent for fulminant hepatitis.

Cathepsins such as cathepsin B and cathepsin L are involved in decomposition of bone collagen in osteoclast. It has been reported that administration of an inhibitor of cathepsins, E-64 or estatin A, to a rat which has an enhanced bone destruction by administration of parathyroid hormone leads to a decrease of calcium concentration and hydroxyproline concentration in blood [Biochemical and Biophysical Research Communication, 125, p.441, (1984); Japanese Patent Publication (kokai) No. 218610/1990]. Accordingly, it is believed that an inhibitor of cathepsins can be a therapeutic agent for osteoporosis, hypercalcemia and the like.

There exist, as a substrate for calpain, sex hormone receptors such as estrogen receptor and androgen receptor, and it is known that calpain activates these receptors. Accordingly, it is considered that an abnormal sthenia of calpain causes a disease which is suspected to be caused by an abnormal activation of the sex hormone receptors, for example, breast carcinoma, prostatic carcinoma or prostatomegaly. It is believed that an inhibitor for calpain can be a therapeutic agent for the above disease.

Receptors for epidermal growth factor (EGF) are also considered to be activated in association with the canceration of cells. It is known that calpain activates the EGF receptors as its substrate. Furthermore, it has been reported that calpain is activated in cells which have been infected with adult T cell human leukocyte virus (ATLV/HTLV-1) [Seikagaku, 57, p.1202, (1985)]. On the other hand, it is said that cathepsin B is greatly involved in a process of cancer metastasis because it accelerates decomposition of collagen which is a important step for the cancer metastasis or directly decomposes collagen, and because it has a profound correlation with plasma membrane of neoplastic cells [Tumor Progression and Markers, p.47, (1982); Journal of Biological Chemistry, 256, p.8536, (1984)]. These facts suggest that a thiol protease inhibitor has an ability to suppress the growth of cancer cells and prevent the metastasis of cancer.

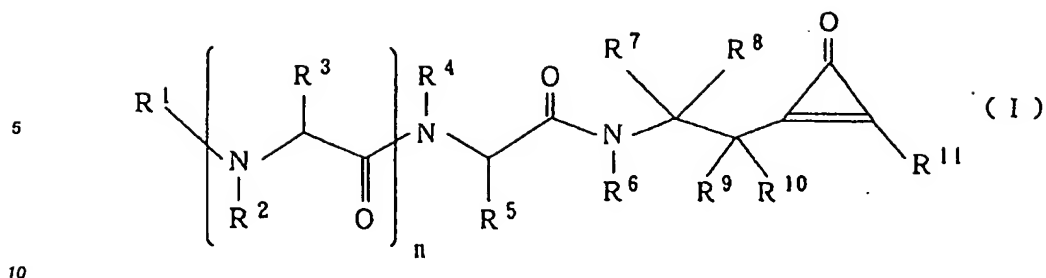
Activation of platelet causes the aggregation thereof which is a cause of thrombus. It has been reported that an inhibitor of calpain, E-64-d, suppressed aggregation of platelet caused by thrombin [Thrombosis Research, 57, p.847, (1990)]. Accordingly, the inhibitor of calpain can be used as an inhibitor against aggregation of platelet.

As described above, an abnormal sthenia of thiol protease causes various diseases and a validity of several thiol protease inhibitors in animal models has been reported. However, most of known inhibitors, for example, epoxy succinate derivatives such as E-64 [Agricultural and Biological Chemistry, 42, p.529, (1978)], E-64-d [Journal of Biochemistry, 93, p.1305, (1983)], NCO-700 [Japanese Patent Publication (kokai) No. 126879/1983], and estatins A and B [The Journal of Antibiotics, 42, p.1362, (1989)], or α -substituted ketone of a peptide such as chloromethyl ketone [Journal of Biochemistry, 99, p.173, (1986)] and acyloxymethyl ketone [Biochemistry, 30, p.4678, (1991)] are irreversible inhibitors. It is generally said that the irreversible inhibitors are highly toxic because they are liable to react with non-specifically to components consisting living body, other than target enzymes. Therefore, there have been few compounds applicable to clinical use so far. Although peptidyl aldehydes such as leupeptin [The Journal of Antibiotics, 22, p.183, (1969)] or carpeptine [Journal of Enzyme Inhibition, 3, p.195, (1990)] are known as reversible inhibitors, they also have problems in chemical and in vivo stabilities, cell membrane permeabilities and the like.

SUMMARY OF THE INVENTION

The present inventors investigated into various compounds with aim of developing reversible inhibitors against thiol protease, which have excellent properties concerning absorbance on oral administration, tissue distribution and cell membrane permeability, and have found that certain derivatives of cyclopropanone have such desired properties.

Thus, the present invention provides cyclopropanone derivatives of general formula (I):



wherein R¹ is hydrogen atom, R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²-SO₂- (in which R¹² is C₁ - C₂₀ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₅ cycloalkyl group, optionally substituted C₆ - C₁₄ aryl group, C₃ - C₁₅ cycloalkyloxy group, optionally substituted C₆ - C₁₄ aryloxy group, optionally substituted C₆ - C₁₄ arylthio group, optionally substituted C₆ - C₁₄ arylsulfonyl group, optionally substituted C₇ - C₂₀ aralkyloxy group, optionally substituted heterocyclic group, oxo group, hydroxyl group, C₁ - C₁₀ alkoxy carbonyl group and carboxyl group; C₃ - C₁₅ cycloalkyl group; optionally substituted C₆ - C₁₄ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁶ each is independently hydrogen atom or C₁ - C₁₀ alkyl group optionally substituted by C₁ - C₅ alkoxy group or C₁ - C₅ alkylthio group; R³, R⁵ and R⁷ each is independently hydrogen atom, C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group or optionally substituted C₇ - C₂₀ aralkyl group; R⁸ is hydrogen atom or C₁ - C₂₀ alkyl group; R⁷ and R⁸ taken together may form C₃ - C₁₅ cycloalkyl group; R⁹ is hydroxyl group or C₂ - C₁₀ acyloxy group; R¹⁰ is hydrogen atom; R⁹ and R¹⁰ taken together may form oxo group; R¹¹ is hydrogen atom, C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₅ cycloalkyl group, C₃ - C₁₅ cycloalkyl group, C₂ - C₂₀ alkenyl group, optionally substituted C₆ - C₁₄ aryl group, optionally substituted C₇ - C₂₀ aralkyl group, optionally substituted heterocyclic group or -C-(R¹³)(R¹⁴)-OH (in which R¹³ and R¹⁴ each is independently hydrogen atom, C₁ - C₂₀ alkyl group, optionally substituted C₇ - C₂₀ aralkyl group or optionally substituted C₆ - C₁₄ aryl group, or R¹³ and R¹⁴ taken together may form C₃ - C₁₅ cycloalkyl group); and n is 0 or 1 or pharmaceutically acceptable salts thereof.

The present invention also provides a pharmaceutical compositions containing, as an active ingredient, a cyclopropenone derivative of formula (I) or a salt thereof.

The present invention also provides a process for the preparation of cyclopropenone derivatives of formula (I).

35 DETAILED DESCRIPTION OF THE INVENTION

Definition:

For the purpose of the invention the following terms used herein are defined as follows:

In the definition of R¹²: examples of C₁ - C₂₀ alkyl group include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, hexyl group, isohexyl group, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, hexadecyl group, heptadecyl group, octadecyl group, nonadecyl group, icosyl group and the like. Such an alkyl group may be optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₅ cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, cyclooctyl group, cyclononyl group, cyclodecyl group, cycloundecyl group, cyclododecyl group, cyclotridecyl group, cyclotetradecyl group, cyclopentadecyl group or the like; C₆ - C₁₄ aryl group such as phenyl group, naphthyl group, anthryl group; C₃ - C₁₅ cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, cyclooctyloxy group, cyclodecyloxy group, cyclopentadecyloxy group or the like; C₆ - C₁₄ aryloxy group such as phenoxy group, 1-naphthoxy group, 2-naphthoxy group or the like; C₆ - C₁₄ arylthio group such as phenylthio group, 1-naphthylthio group, 2-naphthylthio group or the like; C₆ - C₁₄ arylsulfonyl group such as phenylsulfonyl group, 1-naphthylsulfonyl group, 2-naphthylsulfonyl group or the like; C₇ - C₂₀ aralkyloxy group such as benzyloxy group, 1-phenylethoxy group, 2-phenylethoxy group, 1-phenylpropoxy group, 2-phenylpropoxy group, 3-phenylpropoxy group, 4-phenylbutoxy group, 5-phenylpentyloxy group, 1-naphthylmethoxy group, 2-naphthylmethoxy group, 1-(1-naphthyl)ethoxy group, 2-(1-naphthyl)ethoxy group, 1-(2-naphthyl)ethoxy group, 2-(2-naphthyl)ethoxy group or the like; 5 - 10 membered heterocyclic group

containing 1 to 4 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom to form a ring such as furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzoimidazole ring, purine ring, quinolizidine ring, quinoline ring, phthalazine ring, naphthylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, thiazolidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring or the like; C₁ - C₁₀ alkoxy carbonyl group such as methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, hexyloxycarbonyl group, heptyloxycarbonyl group, octyloxycarbonyl group, decyloxycarbonyl group or the like; oxo group; hydroxyl group and carboxyl group. Examples of C₃ - C₁₅ cycloalkyl group, C₆ - C₁₄ aryl group and heterocyclic group are the same as those illustrated in the definition of the substituents of C₁ - C₂₀ alkyl group.

In the definition of R², R⁴ and R⁶, examples of C₁ - C₁₀ alkyl group include methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, hexyl group, isohexyl group, heptyl group, octyl group, nonyl group, decyl group and the like. Such an alkyl group may be optionally substituted by C₁ - C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group or the like or C₁ - C₅ alkylthio group such as methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, tert-butylthio group, pentythio group, isopentythio group or the like.

In the definition of R³, R⁵ and R⁷, examples of C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group and C₃ - C₁₀ cycloalkyl group are the same as those illustrated in the definition of R¹² except that cycloalkyl group is C₃ - C₁₀ cycloalkyl group. Examples of C₇ - C₂₀ aralkyl group are benzyl group, 1-phenethyl group, 2-phenethyl group, 1-phenylpropyl group, 2-phenylpropyl group, 3-phenylpropyl group, 4-phenylbutyl group, 5-phenylpentyl group, 1-naphthylmethyl group, 2-naphthylmethyl group, 1-(1-naphthyl)ethyl group, 1-(2-naphthyl)ethyl group, 2-(1-naphthyl)ethyl group, 2-(2-naphthyl)ethyl group and the like.

In the definition of R⁵, examples of C₁ - C₂₀ alkyl group are the same as those illustrated in the definition of R¹².

Examples of C₃ - C₁₅ cycloalkyl group which R⁷ and R⁸ taken together may form are the same as those illustrated in the definition of R¹².

In the definition of R⁹, examples of C₂ - C₁₀ acyloxy group are alkylcarbonyloxy group such as acetoxy group, propionyloxy group, butyryloxy group, valeryloxy group and the like.

In the definition of R¹¹, examples of C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₅ cycloalkyl group, C₃ - C₁₅ cycloalkyl group, C₆ - C₁₄ aryl group and heterocyclic group are the same as those illustrated in the definition of R¹², and examples of C₂ - C₂₀ alkenyl group are vinyl group, 1-propenyl group, allyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 1-hexenyl group, 2-hexenyl group, 3-hexenyl group, 4-hexenyl group, 5-hexenyl group, 1-heptenyl group, 1-octenyl group, 1-nonenyl group, 1-decenyl group, 1-dodecenyl group, 1-pentadecenyl group and the like. Examples of C₇ - C₂₀ aralkyl group are the same as those illustrated in the definition of R³, R⁵ and R⁷.

In the definition of R¹³ and R¹⁴, examples of C₁ - C₂₀ alkyl group and C₆ - C₁₄ aryl group are the same as those illustrated in the definition of R¹², and examples of C₇ - C₂₀ aralkyl group are the same as those illustrated in the definition of R³, R⁵ and R⁷.

Examples of C₃ - C₁₅ cycloalkyl group which R¹³ and R¹⁴ taken together may form are the same as those illustrated in the definition of R¹².

The aromatic and the heterocyclic groups which positioned at the end of each substituent as defined in the above may optionally have one or more substituents selected from the group consisting of halogen atom such as fluorine atom, chlorine atom, bromine atom or the like; C₁ - C₅ alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl group, neopentyl group or the like;

trifluoromethyl group; C₁ - C₅ alkoxy group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group or the like; C₁ - C₅ alkylendioxy group such as methylenedioxy group, ethylenedioxy group, propylenedioxy

group or the like; hydroxyl group; C₂ - C₆ alkylcarbonyloxy group such as acetoxy group, propionyloxy group, butyryloxy group, valeryloxy group or the like; carboxyl group; C₂ - C₆ alkoxycarbonyl group such as methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group or the like; 5 oxo group; C₂ - C₆ alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, valeryl group or the like; amino group; C₁ - C₅ monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, isopentylamino group or the like; C₂ - C₁₀ dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, diisopropylamino group or 10 the like; C₂ - C₆ alkylcarbonylamino group such as acetylamino group, propionylamino group, isopropionylamino group, butyrylamino group, valerylamino group or the like; carbamoyl group; C₂ - C₆ alkylcarbamoyl group such as methylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, isopropylcarbamoyl group, butylcarbamoyl group, tert-butylcarbamoyl group, pentylcarbamoyl group or the like; C₆ - C₁₄ aryl group such as phenyl group, naphthyl group or the like; and trimethylsilyl group.

15 Although all the compound (I) as defined above are useful for the purpose of the invention, there are some preferable compounds. Thus, compounds (I) included in the following [Group A] are preferable, and among compounds of [group A], those belong to [Group B] are particularly preferred.

[Group A]:

20

Compound of formula (I), wherein R¹ is hydrogen atom, R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²-SO₂- (in which R¹² is C₁ - C₂₀ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₅ cycloalkyl group, optionally substituted C₆ - C₁₄ aryl group, optionally 25 substituted C₆ - C₁₄ aryloxy group, optionally substituted C₆ - C₁₄ arylthio group, optionally substituted C₇ - C₂₀ aralkyloxy group, optionally substituted heterocyclic group, oxo group, hydroxyl group, C₁ - C₁₀ alkoxycarbonyl group and carboxyl group; C₃ - C₁₅ cycloalkyl group, optionally substituted C₆ - C₁₄ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁶ each is independently hydrogen atom, C₁ - C₁₀ alkyl group optionally substituted by C₁ - C₅ alkylthio group; R³, R⁵ and R⁷ each is hydrogen atom, C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group or 30 optionally substituted C₇ - C₂₀ aralkyl group; R⁸ is hydrogen atom or C₁ - C₂₀ alkyl group; R⁹ is hydroxyl group or C₂ - C₁₀ acyloxy group; R¹⁰ is hydrogen atom; or R⁹ and R¹⁰ taken together may form oxo group; R¹¹ is hydrogen atom, C₁ - C₂₀ alkyl group optionally substituted by C₃ - C₁₅ cycloalkyl group, C₃ - C₁₅ cycloalkyl group, C₂ - C₂₀ alkenyl group, optionally substituted C₆ - C₁₄ aryl group, C₇ - C₂₀ aralkyl group, optionally substituted heterocyclic group, or -C(R¹³)(R¹⁴)-OH (in which R¹³ and R¹⁴ each is independently 35 hydrogen atom, C₁ - C₂₀ alkyl group or C₆ - C₁₄ aryl group; and n is 0 or 1.

[Group B]:

Compound of formula (I), wherein R¹ is R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²-SO₂- (in which R¹² is 40 C₁ - C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₀ cycloalkyl group, optionally substituted C₆ - C₁₄ aryloxy group, optionally substituted C₆ - C₁₄ arylthio group, optionally substituted C₇ - C₂₀ aralkyloxy group, optionally substituted heterocyclic group and oxo group; C₃ - C₁₀ cycloalkyl group; optionally substituted C₆ - C₁₀ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁶ each is independently hydrogen atom or C₁ - C₁₀ alkyl 45 group; R³, R⁵ and R⁷ each is independently hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group or optionally substituted C₇ - C₂₀ aralkyl group; R⁸ is hydrogen atom; R⁹ is hydroxyl group or C₂ - C₁₀ acyloxy group; R¹⁰ is hydrogen atom; and R¹¹ is hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group, C₇ - C₂₀ aralkyl group, optionally substituted C₆ - C₁₀ aryl group or optionally substituted 50 heterocyclic group.

Furthermore, among the compounds in [Group B], the compounds belong to [Group C] and [Group D] are preferred and of the compounds in [Group C], those in [Group E] and [Group F] are more preferred. Among compounds in [Group D], those in [Group G] are more preferred.

55 [Group C]:

Compounds of formula (I), wherein R¹ is R¹²-CO-, R¹²-O-CO- or R¹²-NH-CO- (in which R¹² is C₁ - C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ -

C₁₀ cycloalkyl group, optionally substituted C₆ - C₁₄ aryl group, optionally substituted C₆ - C₁₄ aryloxy group, optionally substituted C₆ - C₁₄ arylthio group, optionally substituted C₇ - C₂₀ aralkyloxy group, optionally substituted heterocyclic group and oxo group; or optionally substituted C₆ - C₁₀ aryl group); R², R⁴ and R⁶ each is independently hydrogen atom or C₁ - C₁₀ alkyl group; R³, R⁵ and R⁷ each hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group or C₇ - C₂₀ aralkyl group; R⁸ is hydrogen atom; R⁹ is hydroxyl group or C₂ - C₁₀ acyloxy group; R¹⁰ is hydrogen atom; and R¹¹ is hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group, C₇ - C₂₀ aralkyl group, optionally substituted C₆ - C₁₀ aryl group or optionally substituted heterocyclic group.

[Group D]:

Compounds of formula (I), wherein R¹ is R¹²-SO₂-(in which R¹² is C₁ - C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₀ cycloalkyl group, optionally substituted C₆ - C₁₄ aryl group, optionally substituted C₆ - C₁₄ aryloxy group, C₆ - C₁₄ arylthio group, optionally substituted C₇ - C₂₀ aralkyloxy group, optionally substituted heterocyclic group and oxo group; C₃ - C₁₀ cycloalkyl group; optionally substituted C₆ - C₁₀ aryl group or optionally substituted heterocyclic group); and R¹¹ is hydrogen atom, optionally substituted C₆ - C₁₀ aryl group or optionally substituted heterocyclic group.

[Group E]:

Compounds of formula (I), wherein R¹ is R¹²-O-CO-(in which R¹² is C₁ - C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₀ cycloalkyl group, C₆ - C₁₄ aryl group and heterocyclic group or C₃ - C₁₀ cycloalkyl group); R⁴ and R⁶ each is hydrogen atom; R¹¹ is hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group, C₃ - C₁₀ cycloalkyl group, C₇ - C₂₀ aralkyl group or C₆ - C₁₀ aryl group; and n is 0.

[Group F]:

Compound of formula (I), wherein R¹ is R¹²-O-CO-(in which R¹² is C₁ - C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃ - C₁₀ cycloalkyl group, C₆ - C₁₄ aryl group, and heterocyclic group); R⁴ and R⁶ each is hydrogen atom; R⁵ and R⁷ each is independently hydrogen atom, C₁ - C₁₅ alkyl group optionally substituted by C₃ - C₁₀ cycloalkyl group or C₇ - C₂₀ aralkyl group; R⁹ is hydroxyl group; R¹⁰ is hydrogen atom; R¹¹ is optionally substituted heterocyclic group; and n is 0.

[Group G]:

Compounds of formula (I), wherein R¹² is optionally substituted C₆ - C₁₀ aryl group or optionally substituted heterocyclic group.

As will be understood from the structure, the cyclopropanone derivatives of formula (I) can form pharmaceutically acceptable salts thereof. Examples of such salts include, when an acidic group is present, metal salts such as lithium salt, sodium salt, potassium salt, magnesium salt, calcium salt or the like and ammonium salts such as ammonium salt, methylammonium salt, dimethylammonium salt, trimethylammonium salt, dicyclohexylammonium salt or the like and, when a basic group is present, mineral acid salts such as hydrochloride, hydrobromide, sulfate, nitrate, phosphate or the like and organic acid salts such as methanesulfonate, benzenesulfonate, p-toluenesulfonate, acetate, propionate, tartrate, fumarate, maleate, malate, oxalate, succinate, citrate, benzoate, mandelate, cinnamate, lactate or the like.

Considering the stereochemistry of the sites of double bond existing in the cyclopropanone derivatives of formula (I), these compounds can take (E), (Z) or (EZ) form. As to the stereochemistry of asymmetric carbon, compounds (I) can be independently in (R), (S) or (RS) form.

The following Tables 1 and 2 shows examples of the cyclopropanone derivatives of formula (I) in case of n = 0 and n = 1, respectively.

Table 1 (n=0)

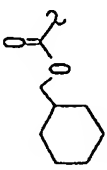
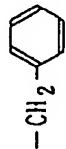
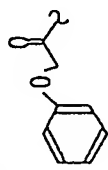
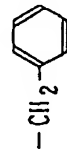
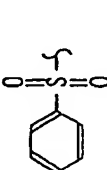
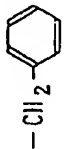
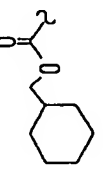

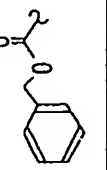

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1		H		H	-CH ₃	H	-OH	H	H
2		H		H	-CH ₃	H	-OH	H	H
3		H		H	-CH ₃	H	-OH	H	H
4		H		H	-CH(CH ₃) ₂	H	-OH	H	H
5		H		-CH ₃	-CH(CH ₃) ₂	H	-OH	H	H

Table 1 (n=0) (continued)

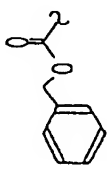
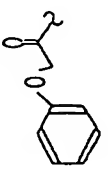
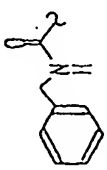
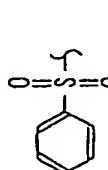
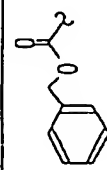
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
6		-CH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
10		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	H

Table 1 (n=0) (continued)

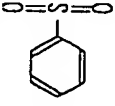
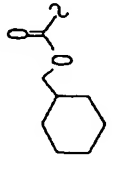

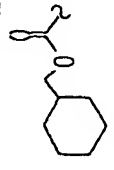
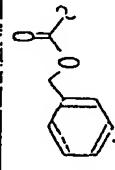
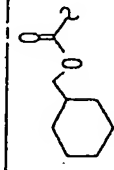
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	H
1 2		H		H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	H
1 3		H	-CH ₃	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
1 4		H	-CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
1 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H

Table 1 (n=0) (continued)

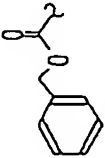
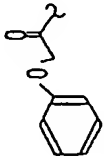
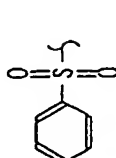
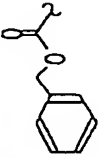

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
16		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
17	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
18		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
19		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
20		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H		H	H

Table 1 (n=0) (continued)

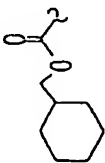
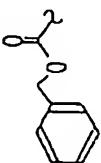

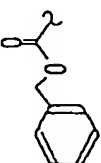


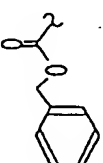
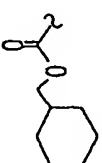

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	H
2 2		H	-CH ₂ - 	H	-CH ₃	-CH ₃	-OH	H	H
2 3		H	-CH ₂ - 	H	-CH ₃	-CH ₃		H	H
2 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ -	-OH	H	H
2 5		H	-CH(CH ₃) ₂	H	-CH ₂ - 	H	-OH	H	H

Table 1 (n=0) (continued)

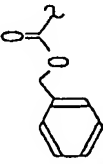

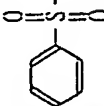

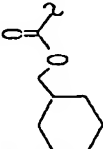


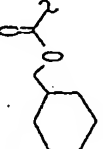

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ - 	H	-OH	H	H
2 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ - 	H	-OH	H	H
2 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ - 	H	-OH	H	H
2 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	-CH ₃
3 0		H	-CH ₂ - 	H	-CH ₃	H	-OH	H	-CH ₃

Table 1 (n=0) (continued)

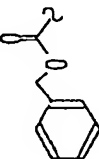
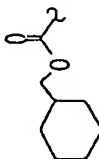
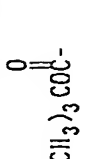
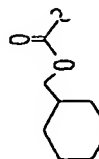
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	-CH ₃
3 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	-CH ₃
3 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
3 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
3 5	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃

Table 1 (n=0) (continued)

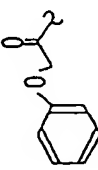
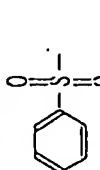
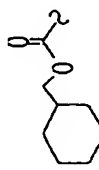
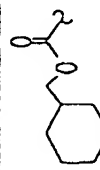
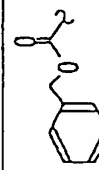
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
3 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
3 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
3 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₂ CH ₃
4 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	-CH ₂ CH ₃

Table 1 (n=0) (continued)

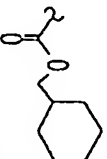
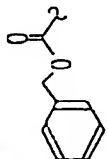
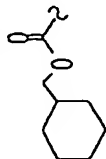

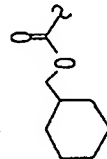
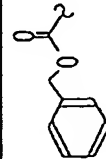

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₂ CH ₃
4 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	-CH ₂ CH(CH ₃) ₂
4 3		H		H	-CH ₃	H	-OH	H	-CH ₂ CH ₂ CH(CH ₃) ₂
4 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₂ CH ₂ CH(CH ₃) ₂
4 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 6		H		H	-CH ₃	H	-OH	H	
4 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 8		H		H	-CH ₃	H	-OH	H	
4 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	
5 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
5 1		H		H	-CH ₃	H	-OH	H	
5 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
5 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
5 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
5 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
5 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
5 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
5 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
5 9		H		H	-CH ₃	H	-OH	H	
6 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

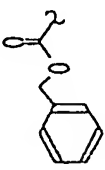

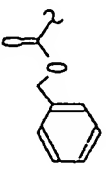

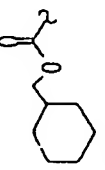

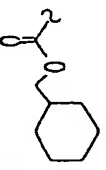


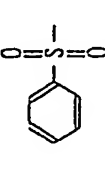


Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
6 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
6 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
6 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	
6 4		H	-CH ₂ - 	H	-CH ₃	H	-OH	H	
6 5		H	-CH ₂ - 	H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

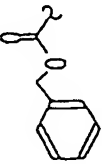

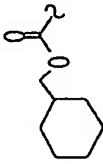

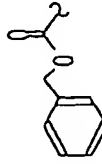



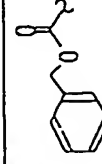

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
6 6		H	H	H	-CH(CH ₃) ₂	H	-OH	H	
6 7		H	-CH ₃	H	-CH(CH ₃) ₂	H	-OH	H	
6 8		H	-CH ₃	H	-CH(CH ₃) ₂	H	-OH	H	
6 9		H	-CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 0		H	-CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)



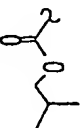

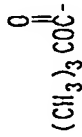





Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
7 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
7 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
7 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H		H	
7 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H			
8 0		H	-CH ₂ CH(CH ₃) ₂	CH ₃	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

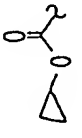
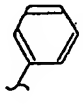

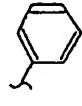
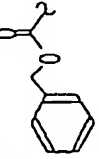
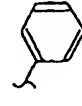
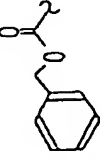
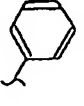
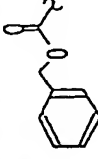
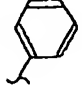
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
8 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
8 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
8 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
8 4		H	-CH ₂ CH(CH ₃) ₂	-CH ₃	-CH(CH ₃) ₂	H	-OH	H	
8 5		-CH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

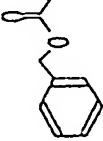

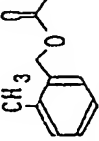

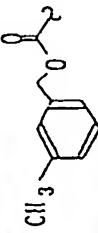

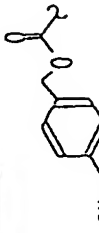

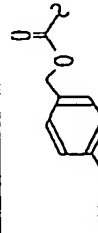

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
8 6		-CH ₃	-CH ₂ CH(CH ₃) ₂	-ClI ₃	-CH(CH ₃) ₂	H	-OH	H	
8 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
8 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
8 9		H	-ClI ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
9 0		H	-ClI ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
9 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
9 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
9 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
9 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
9 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)



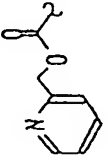

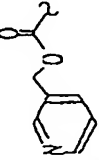

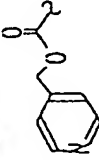

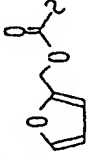

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
96		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
97		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
98		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
99		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
100		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

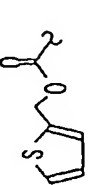

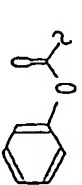

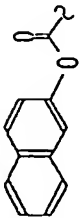

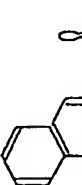


Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
101		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
102		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
103		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
104		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
105	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

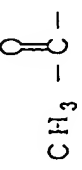

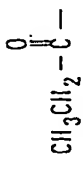

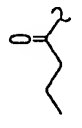





Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 0 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 0 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 0 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 0 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 1 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

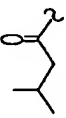
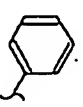
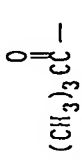
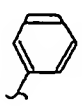

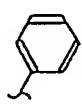

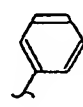
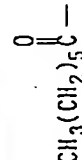
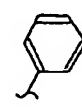
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
111		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
112		H	-CH ₂ CH(ClCH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
113		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
114		H	-CH ₂ CH(ClCH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
115		H	-CH ₂ CH(ClCH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)






Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
116	$\text{CH}_3(\text{CH}_2)_6\overset{\text{O}}{\parallel}\text{C}-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	
117	$\text{CH}_3(\text{CH}_2)_7\overset{\text{O}}{\parallel}\text{C}-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	
118	$\text{CH}_3(\text{CH}_2)_8\overset{\text{O}}{\parallel}\text{C}-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	
119	$\text{CH}_3(\text{CH}_2)_9\overset{\text{O}}{\parallel}\text{C}-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	
120	$\text{CH}_3(\text{CH}_2)_{10}\overset{\text{O}}{\parallel}\text{C}-$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 2 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)





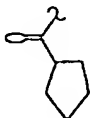

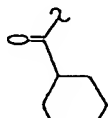

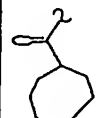

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 2 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 2 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 3 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

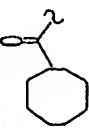



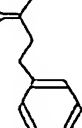



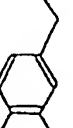

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
131		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
132		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
133		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
134		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
135		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

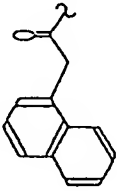

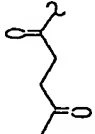

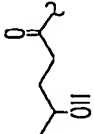



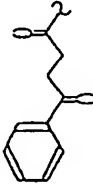

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 3 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 3 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 3 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 3 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 4 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

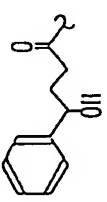

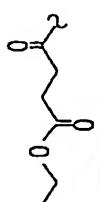

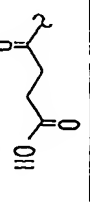



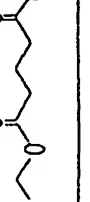

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 4 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 4 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 4 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 4 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 4 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
146		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
147		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
148		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
149		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
150		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

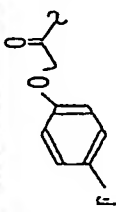

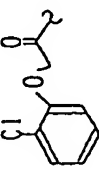

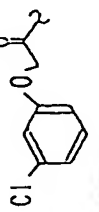



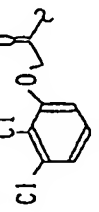

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 5 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 5 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 5 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 6 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
161		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
162		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
163		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
164		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
165		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)


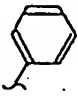
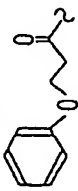
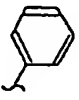

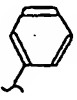

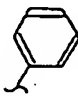
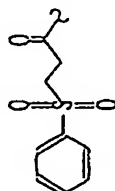
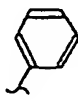
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 6 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 6 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 6 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 6 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 7 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

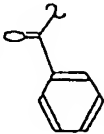

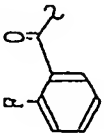

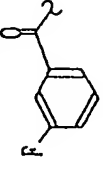

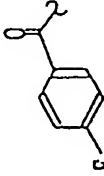

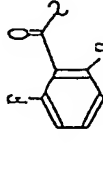

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
171		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
172		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
173		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
174		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
175		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 7 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 7 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 7 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 7 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 8 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
181		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
182		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
183		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
184		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
185		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
1 8 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 8 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 8 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 8 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
1 9 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

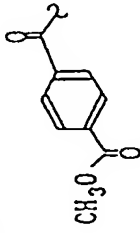

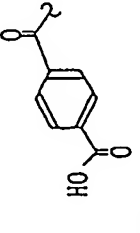

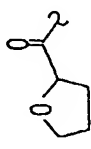

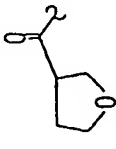

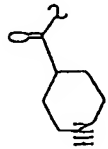

Compd. No.	R1	R4	R5	R6	R7	R8	R9	R10	R11
191		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
192		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
193		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
194		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
195		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

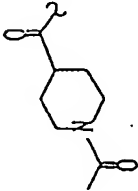

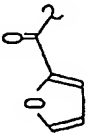

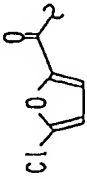

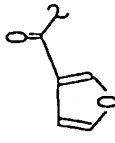

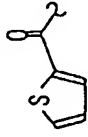

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
196		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
197		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
198		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
199		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
200		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

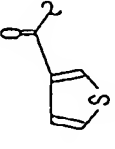
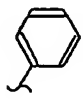
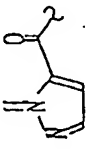
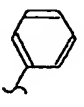
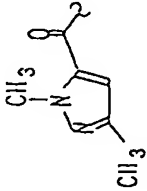
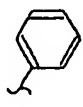
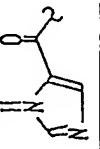
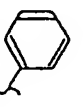
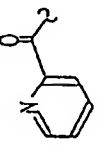
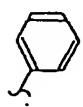
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
201		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
202		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
203		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
204		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
205		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
206		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
207		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
208		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
209		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
210		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 1 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

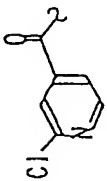
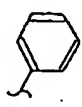
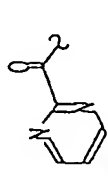
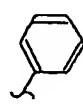
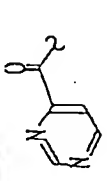
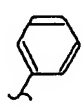
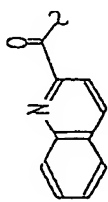
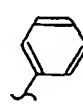
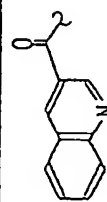
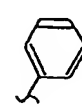
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 1 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 1 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

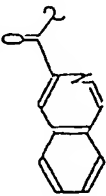

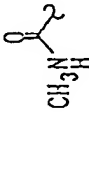

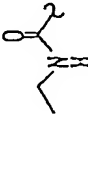



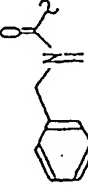

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 2 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

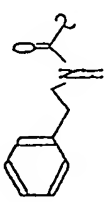

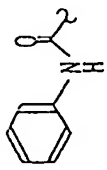

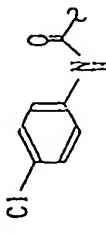

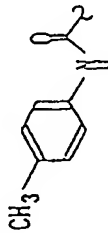

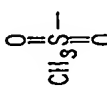

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 2 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 2 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 3 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

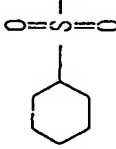
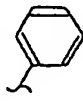
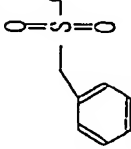
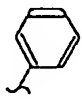
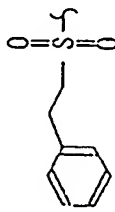
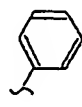
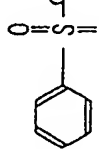
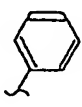
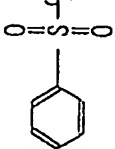
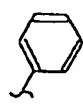
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 3 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 3 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 0		H	-CH ₂ CH(CH ₃) ₂	-CH ₃	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 4 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H		H	
2 4 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H			
2 4 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

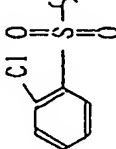
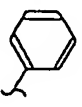
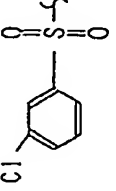
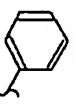
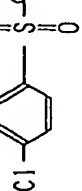
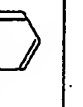
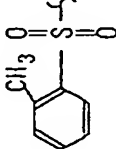
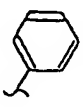
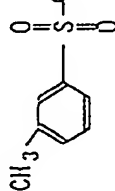
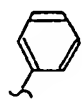
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 4 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 4 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 5 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

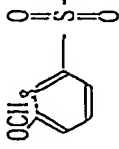

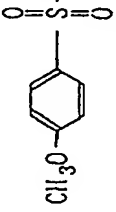

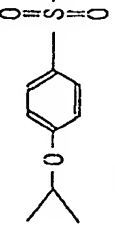

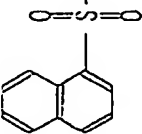

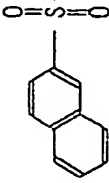

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 5 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 5 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 6 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

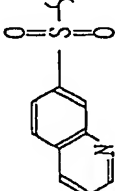
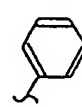
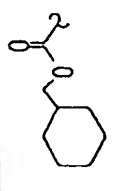
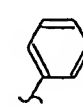
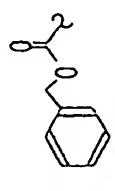
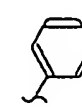
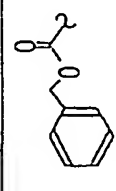
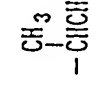
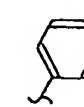
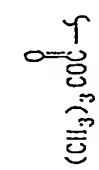

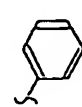
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 6 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 7		H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 8		H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-CH(CH ₃) ₂	H	-OH	H	
2 6 9		H		H	-CH(CH ₃) ₂	H	-OH	H	
2 7 0		H		H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

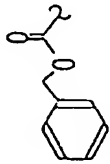




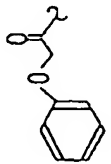


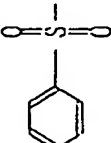


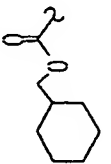


Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹	
271		H		H	-CH ₂ -	H	-CH(CH ₃) ₂	H	-OH	
272	H	H		H	-CH ₂ -	H	-CH(CH ₃) ₂	H	-OH	
273		H		H	-CH ₂ -	H	-CH(CH ₃) ₂	H	-OH	
274		H		H	-CH ₂ -	H	-CH(CH ₃) ₂	H	-OH	
275		H		H	-CH ₂ -	H	-CH(CH ₃) ₂	H	-OH	

Table 1 (n=0) (continued)

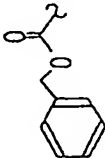
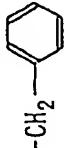

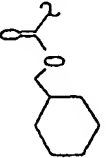

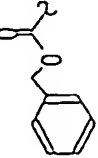

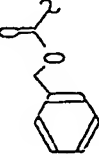

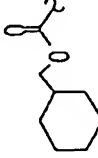

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
276		H		H	$-\text{CH}(\text{CH}_3)_2$	H	-OH	H	
277		H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	-OH	H	
278		H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	-OH	H	
279		H	$-\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	H	-OH	H	
280		H	$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	H	$-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$	H	-OH	H	

Table 1 (n=0) (continued)

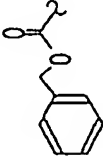

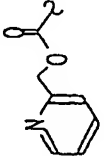

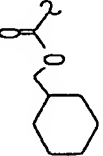


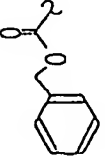


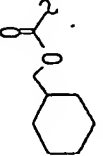
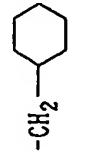

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
281		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
282		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
283		H	-CH ₂ CH(CH ₃) ₂	H		H	-OH	H	
284		H	-CH ₂ CH(CH ₃) ₂	H		H	-OH	H	
285		H	-CH ₂ CH(CH ₃) ₂	H		H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R1	R4	R5	R6	R7	R8	R9	R10	R11
286		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
287		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
288		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
289		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
290		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	

Table 1 (n=0) (continued)

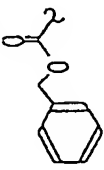

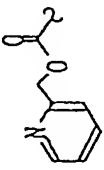

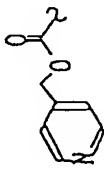


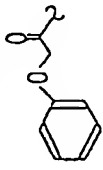

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 9 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 4	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	

Table 1 (n=0) (continued)

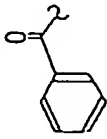

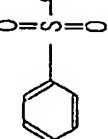

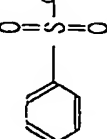

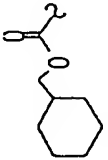


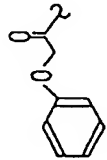


Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
2 9 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 8		-CH ₂ SCCH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃	-OH	H	
2 9 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃			
3 0 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃			

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 0 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	-CH ₃			
3 0 2		H	-CH ₂ CH(CH ₃) ₂	H	- (CH ₂) ₅ -	-	-OH	H	
3 0 3		H	-CH ₂ CH(CH ₃) ₂	H	- (CH ₂) ₅ -	-	-OH	H	
3 0 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 0 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

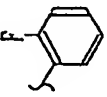
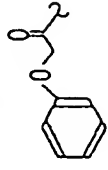
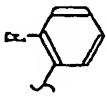
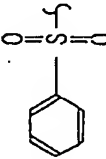
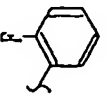
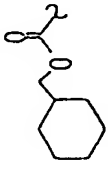
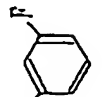
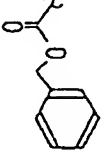
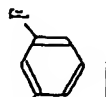
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
306	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
307		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
308		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
309		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
310		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

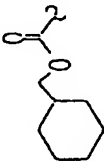
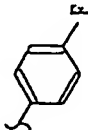
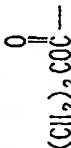
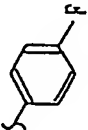
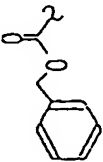
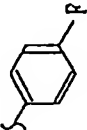
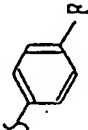
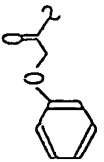
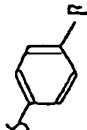
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 1 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 1 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 1 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 1 4	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 1 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

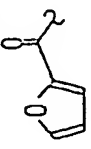
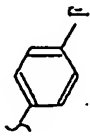
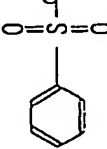
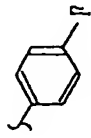
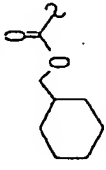
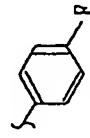
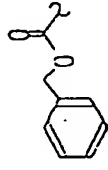
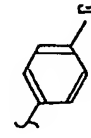
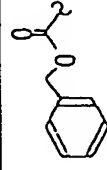

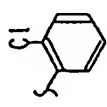
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
316		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
317		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
318		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
319		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
320		H	-CH ₂ - 	H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 2 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 2 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 2 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 2 4		H		H	-CH ₃	H	-OH	H	
3 2 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 2 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 2 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 2 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 2 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 3 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 3 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 3 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 3 3	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 3 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 3 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

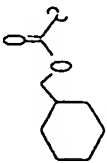
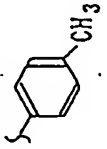
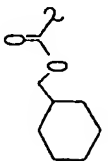
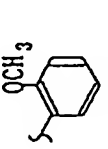
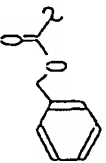
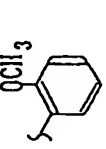
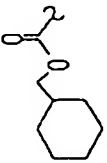
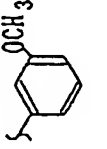
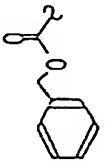
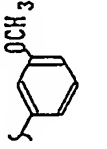
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 3 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 3 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 3 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 3 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 4 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

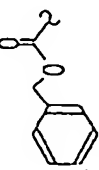
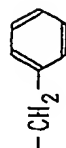
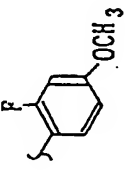
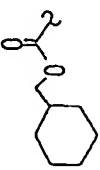
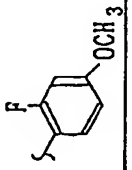
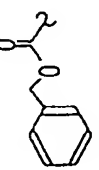
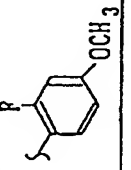
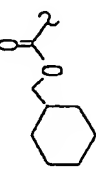
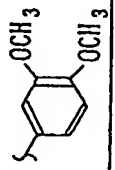
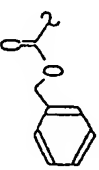
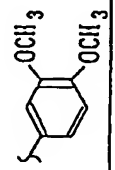
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 4 1		H		H	-CH ₃	H	-OH	H	
3 4 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	
3 4 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	
3 4 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 4 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

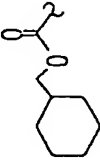
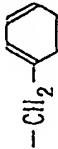
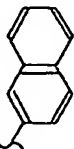
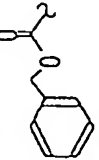
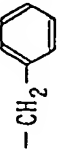
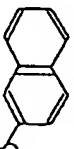
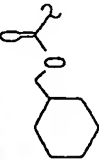
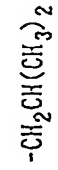
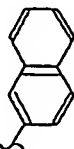
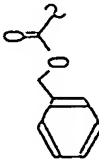
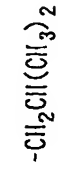
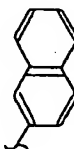

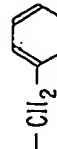
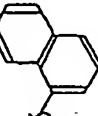
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
346		H		H	-CH ₃	H	-OH	H	
347		H		H	-CH ₃	H	-OH	H	
348		H		H	-CH(CH ₃) ₂	H	-OH	H	
349		H		H	-CH(CH ₃) ₂	H	-OH	H	
350		H		H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 5 1		H		H	-CH ₃	H	-OH	H	
3 5 2		H		H	-CH(CH ₃) ₂	H	-OH	H	
3 5 3		H		H	-CH(CH ₃) ₂	H	-OH	H	
3 5 4		H		H	-CH ₃	H	-OH	H	
3 5 5		H		H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 5 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	
3 5 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 5 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 5 9	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

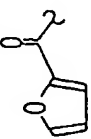

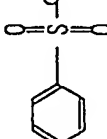

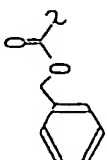

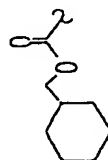
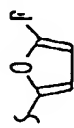
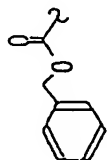
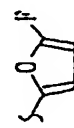
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 6 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 6 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

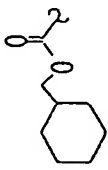
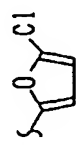
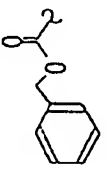
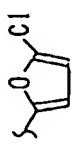
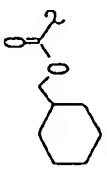
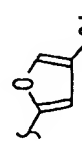
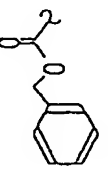
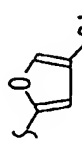
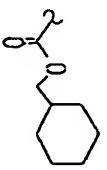
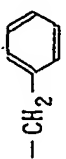

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 6 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 6 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 7 0		H		H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

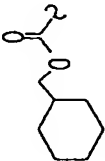
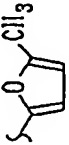
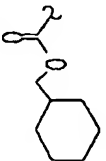
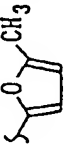
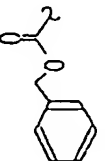

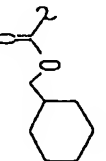

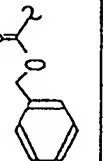
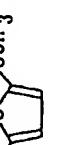
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 7 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	
3 7 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 7 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 7 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 7 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 7 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 7 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 7 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 7 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 8 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 8 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 8 2		H		H	-CH ₃	H	-OH	H	
3 8 3		H	-CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 8 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 8 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 8 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 8 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 8 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
3 8 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 9 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
3 9 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
3 9 9		H		H	-CH ₃	H	-OH	H	
4 0 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

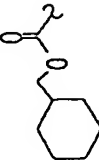
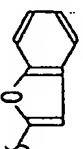
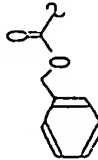
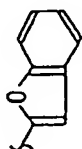
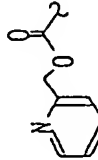
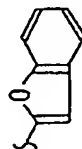
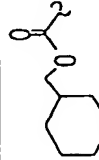

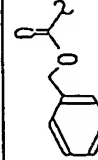

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
401		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
402		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
403		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
404		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
405		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
406		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
407		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
408		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
409		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	-CH ₂ OH
410		H		H	-CH ₃	H	-OH	H	-CH ₂ OH

Table 1 (n=0) (continued)

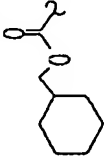
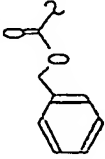
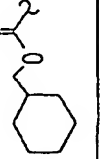
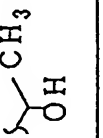

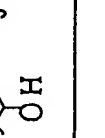

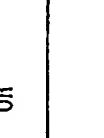
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 1 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	-CH ₂ OH
4 1 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	-CH ₂ OH
4 1 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 1 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 1 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
416		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
417		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	
418		H		H	-CH ₃	H	-OH	H	
419		H	-CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
420		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 2 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 4	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

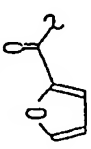

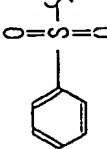

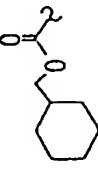

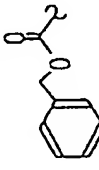

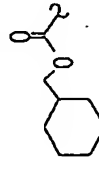
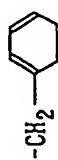

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 2 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 2 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
4 2 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
4 3 0		H	-CH ₂ CH(CH ₃) ₂	H		H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 3 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 3 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 3 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 3 4	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 3 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

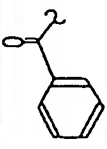

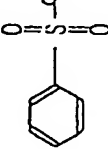

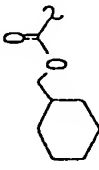

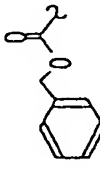
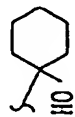

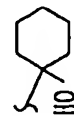
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
436		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
437		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
438		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
439		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
440		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

Table 1 (n=0) (continued)

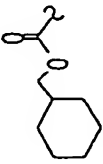

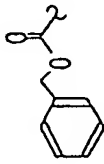

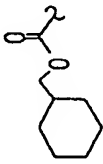
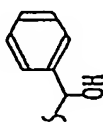
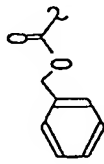
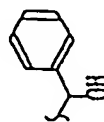
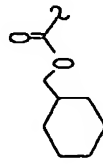
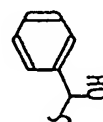
Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 4 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 4 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 4 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 4 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 4 5		H	-CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	

Table 1 (n=0) (continued)

Compd. No.	R ¹	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 4 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	
4 4 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 4 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 2 (n=1)

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 4 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	H
4 5 0		H	-CH ₂ CH(CH ₃) ₂	H		H	-CH ₃	H	-OH	H	H
4 5 1		H	-CH ₂ CH(CH ₃) ₂	H		H	-CH ₃	H	-OH	H	H
4 5 2		H	-CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
4 5 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H

Table 2 (n=1) (continued)

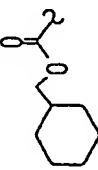

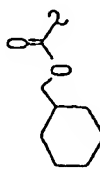
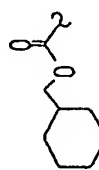
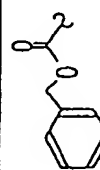
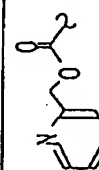
Compd. No.	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11
4 5 4		H	 -CH ₂ -	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	H
4 5 5		H	-CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
4 5 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
4 5 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H
4 5 8		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	H

Table 2 (n=1) (continued)

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 5 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	H
4 6 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
4 6 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
4 6 2		H	-CH ₂ -	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	-CH ₃
4 6 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H	-OH	H	

Table 2 (n=1) (continued)

Compd. No.	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11
4 6 4		H	-CH2CH(CH3)2	H	-CH2-	H	-CH3	H	-OH	H	
4 6 5		H	-CH(CH3)2	H	-CH(CH3)2	H	-CH(CH3)2	H	-OH	H	
4 6 6		H	-CH(CH3)2	H	-CH2CH(CH3)2	H	-CH(CH3)2	H	-OH	H	
4 6 7		H	-CH2CH(CH3)2	H	-CH2CH(CH3)2	H	-CH(CH3)2	H	-OH	H	
4 6 8		H	-CH2CH(CH3)2	H	-CH2CH(CH3)2	H	-CH(CH3)2	H	-OH	H	

Table 2 (n=1) (continued)

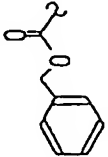

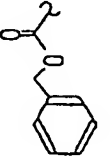

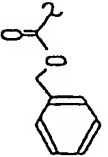

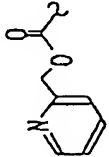


Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 6 9		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 7 0		-CH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 7 1		H	-CH ₂ CH(CH ₃) ₂	-CH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 7 2		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 7 3	H	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 2 (n=1) (continued)

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
474		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
475		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
476		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
477		H	-CH ₂ -	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
478		H	-CH ₂ -	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

Table 2 (n=1) (continued)

Compd. No.	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11
479		H	-CH2CH(CH3)2	H	-CH2CH2CH2CH3	H	-CH(CH3)2	H	-OH	H	
480		H	-CH3	H		H	-CH(CH3)2	H	-OH	H	
481		H	-CH2CH(CH3)2	H		H	-CH(CH3)2	H	-OH	H	
482		H	-CH2CH(CH3)2	H	-CH(CH3)2	H	-CH2CH2CH2CH3	H	-OH	H	
483		H	-CH2CH(CH3)2	H	-CH2CH(CH3)2	H	-CH2CH2CH2CH3	H	-OH	H	

Table 2 (n=1) (continued)

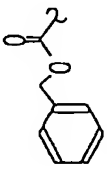
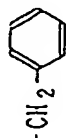

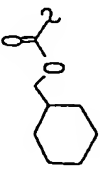
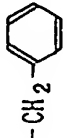

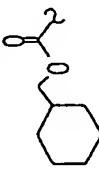
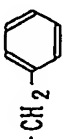

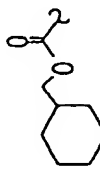
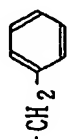

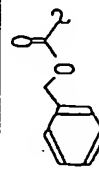
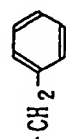

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 8 4		H		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
4 8 5		H	-CH ₂ CH(CH ₃) ₂	H		H	-CH ₂ CH(CH ₃) ₂	H	-OH	H	
4 8 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₃	H		H	-OH	H	
4 8 7		H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H		H	-OH	H	
4 8 8		H	-CH ₃	H	-CH ₂ CH(CH ₃) ₂	H		H	-OH	H	

Table 2 (n=1) (continued)

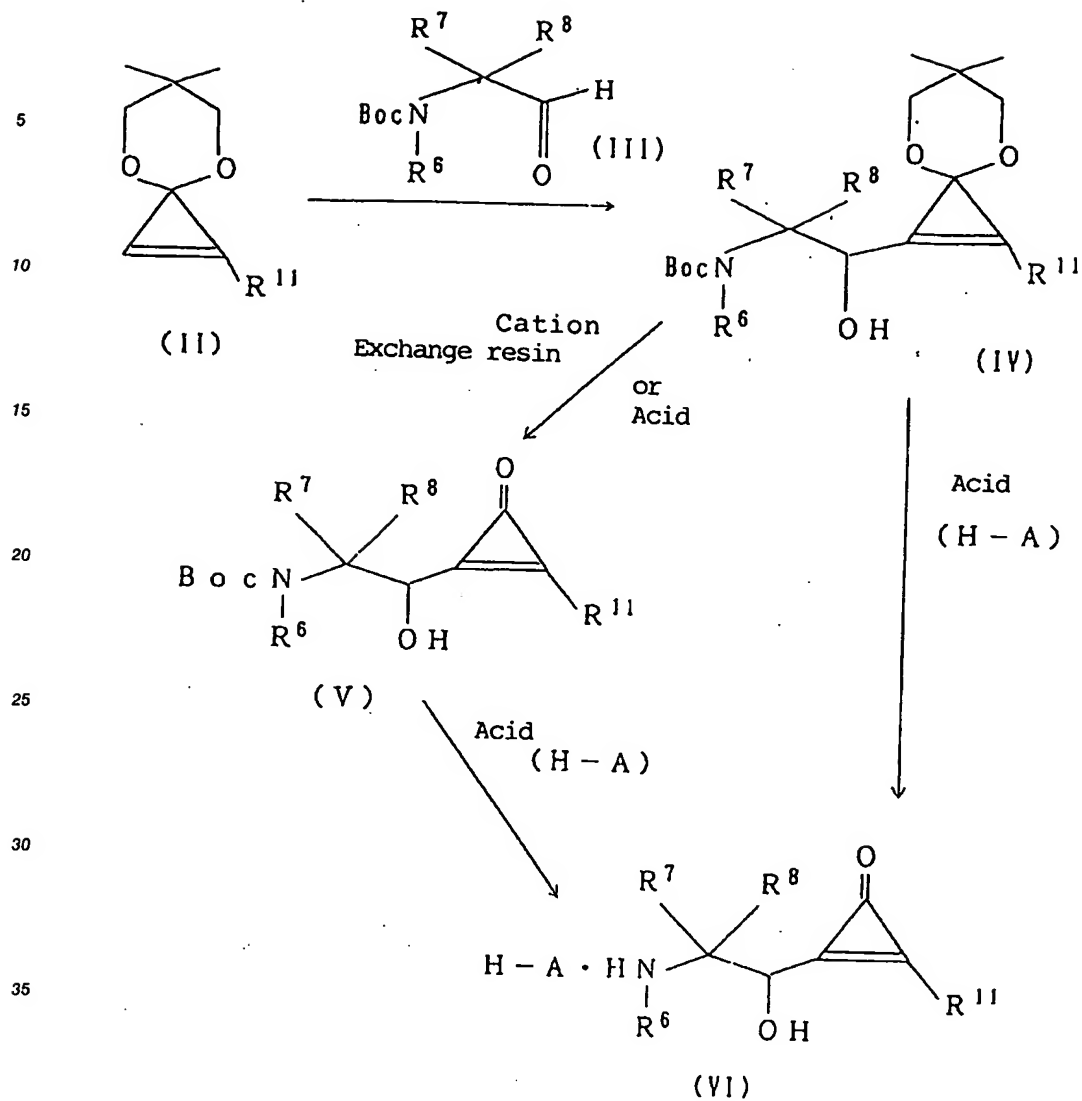
Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 8 9		H	-CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
4 9 0		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
4 9 1		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
4 9 2		-CH ₃	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ -	H	-OH	H	
4 9 3		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	

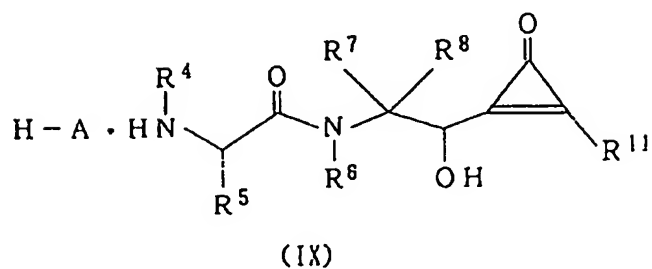
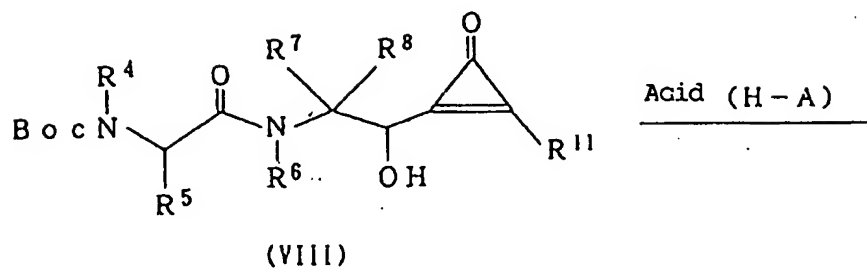
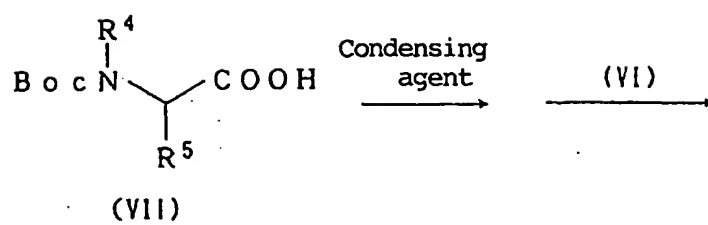
Table 2 (n=1) (continued)

Compd. No.	R ¹	R ²	R ³	R ⁴	R ⁵	R ⁶	R ⁷	R ⁸	R ⁹	R ¹⁰	R ¹¹
4 9 4		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH ₂ CH ₂ CH ₃	H	-OH	H	
4 9 5		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	
4 9 6		H	-CH ₂ CH(CH ₃) ₂	H	-CH ₂ CH(CH ₃) ₂	H	-CH(CH ₃) ₂	H	-OH	H	

The compound (I) of the invention can be prepared using any of known methods. However, there are some preferable methods as will be hereinafter explained in detail.

Production 1:

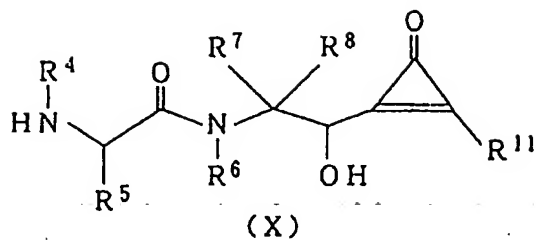




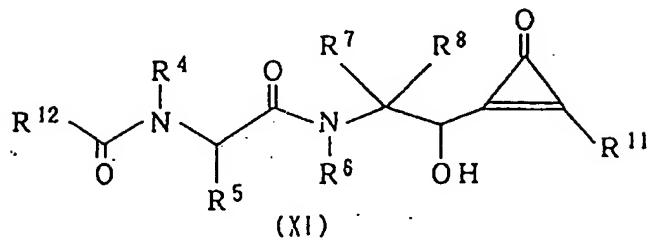
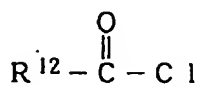
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Neutralization

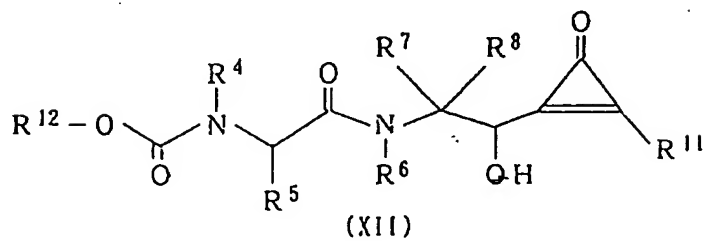
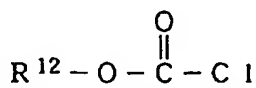
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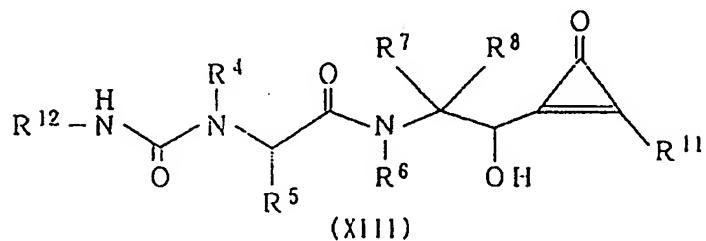
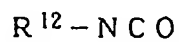
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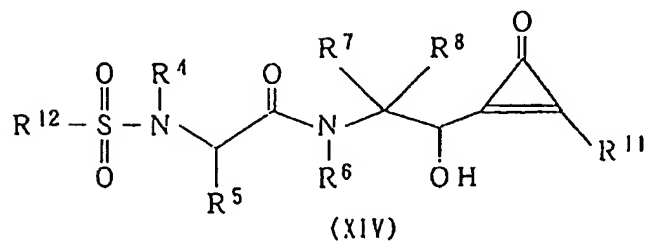
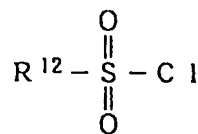
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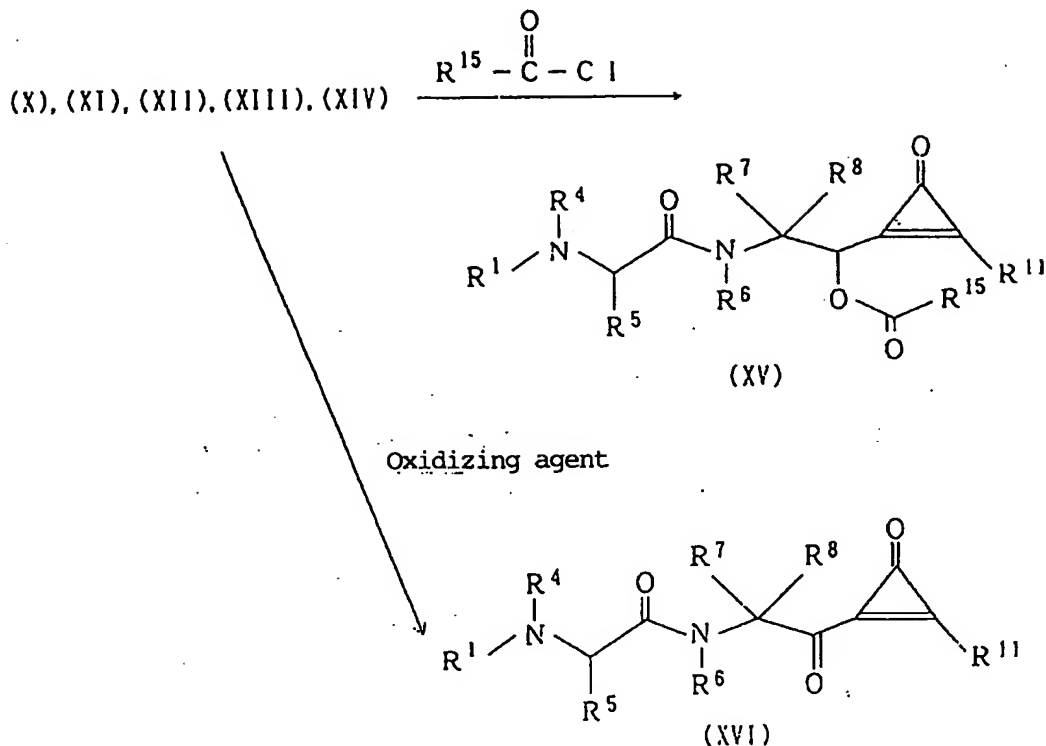


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(wherein R^1 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} and R^{12} are as defined above, and R^{15} is $C_1 - C_9$ alkyl group, Boc is tert-butoxycarbonyl group).

The compound of the general formula (IV) above can be prepared by dissolving the cyclopropenone ketal of the general formula (II) above, readily available by known method [Tetrahedron Letters, 32, 1339 (1991)], in ethereal solvent such as tetrahydrofuran, diethyl ether or the like and adding strong base such as n-butyllithium, methyllithium, lithium diisopropylamide or the like in the presence of an additive such as N,N,N', N'-tetramethylethylenediamine, hexamethylphosphoric triamide, 1,3-dimethyl-2-imidazolidone or the like at -40°C to -100°C to give a lithio compound, which is followed by the addition of tert-butoxycarbonylaminoaldehyde derivative of formula (III). In this reaction, the aldehyde of the general formula (III) above may be added to the cerium salt of lithio compound which previously produced by adding a suspension of anhydrous cerium chloride in tetrahydrofuran, n-hexane or the like to said lithio compound.

Then, the compound (IV) is treated with a cation exchange resin such as Amberlist 15^R or with a mineral acid such as dilute sulfuric acid in order to selective deprotection of ketal so that the cyclopropenone derivative of the general formula (V) above can be obtained. Further, the compound (V) is allowed to react with a mineral acid such as hydrochloric acid, sulfuric acid or the like or an organic acid such as p-toluenesulfonic acid, methanesulfonic acid or the like, in a solvent such as dichloromethane, chloroform, dioxane, ethyl acetate or the like to isolate an amine salt (VI) as a stable compound.

Alternatively, the amine salt (VI) can be prepared in one step by reacting the compound of the general formula (IV) above with a mineral acid such as hydrogen chloride, hydrogen bromide, sulfuric acid or the like or an organic acid such as p-toluenesulfonic acid, methanesulfonic acid or the like in a solvent such as dichloromethane, chloroform, dioxane, ethyl acetate or the like with simultaneous deprotection of both of the ketal and tert-butoxycarbonyl group.

Then, the cyclopropenone derivatives of the general formula (VIII) above can be prepared by activating the N-substituted amino acid derivative of the general formula (VII) above with a condensing agent such as isobutyl chloroformate, diphenylphosphorylazide, carbonyldiimidazole, oxalyl chloride, dicyclohexylcarbodiimide or the like, if necessary, in the presence of an amine such as triethylamine, pyridine or the like, reacting it with the amine salt of the general formula (VI) obtained above and a base such as triethylamine, pyridine or the like.

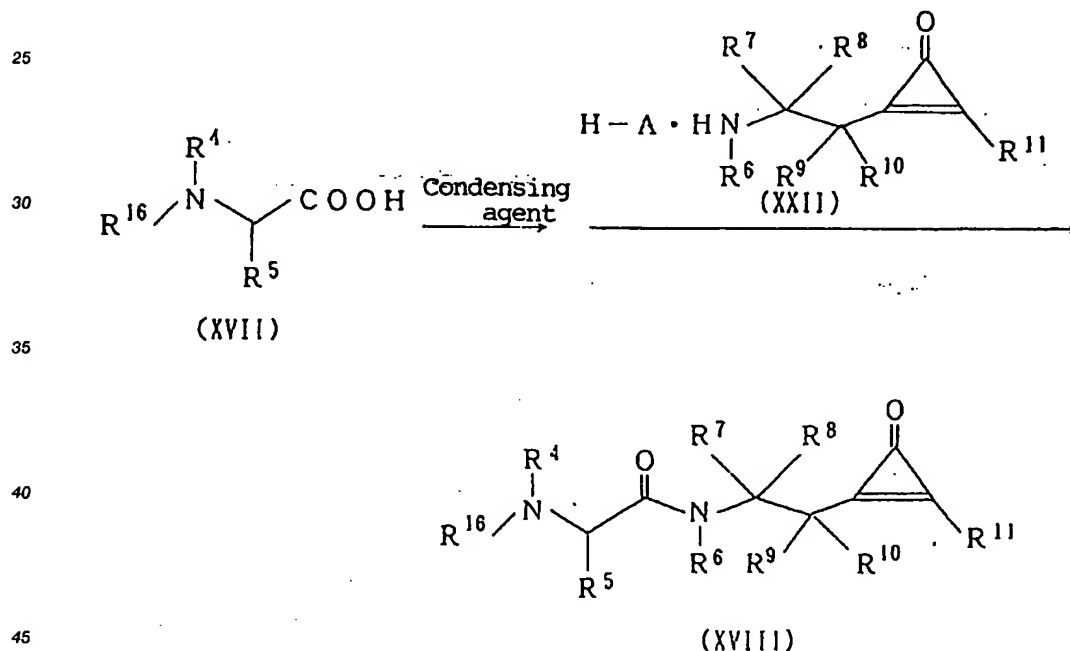
Further, the amine salt of the general formula (IX) above can be obtained by treating with a mineral acid

such as hydrogen chloride, hydrogen bromide, sulfuric acid, nitric acid or the like or an organic acid such as p-toluenesulfonic acid, methanesulfonic acid or the like to deprotect the tert-butoxycarbonyl group. Then, the compound of the general formula (XI) above can be prepared by reacting the compound (IX) with the acyl chloride of the formula $R^{12}\text{-CO-Cl}$ in the presence of an amine such as triethylamine, pyridine or the like in an organic solvent such as chloroform, methylene chloride, ethyl acetate, dimethylformamide or the like.

Similarly, the compound (XII) can be prepared by reacting the compound (IX) with the chloroformic acid derivative of the formula $R^{12}\text{-O-CO-Cl}$ and the compound (XIII) by reacting the compound (IX) with the isocyanate of the formula $R^{12}\text{-NCO}$, and the compound (XIV) by reacting the compound (IX) with the sulfonyl chloride of the formula $R^{12}\text{-SO}_2\text{-Cl}$. The compound (X) can be prepared by neutralizing the compound (IX) with an alkali such as lithium hydroxide, potassium hydroxide, sodium hydroxide or the like or an anion exchange resin.

Further, the compound of the general formula (XV) above can be prepared by reacting the compound (X) - (XIV) with the acyl chloride of the formula $R^{15}\text{-CO-Cl}$ in the presence of an amine such as triethylamine, pyridine or the like in a solvent such as dichloromethane, chloroform, 1,2-dichloroethane or the like. The cyclopropenone derivative of the general formula (XVI) above can be prepared by oxidizing the hydroxy group of cyclopropenone derivative of formula (X) - (XIV) with a conventional oxidizing agent such as sulfur trioxide-pyridine complex-dimethyl sulfoxide, oxalyl chloride-dimethyl sulfoxide, acetic anhydride-dimethyl sulfoxide, N-chlorosuccinimide, chromium chloride-pyridine complex or the like.

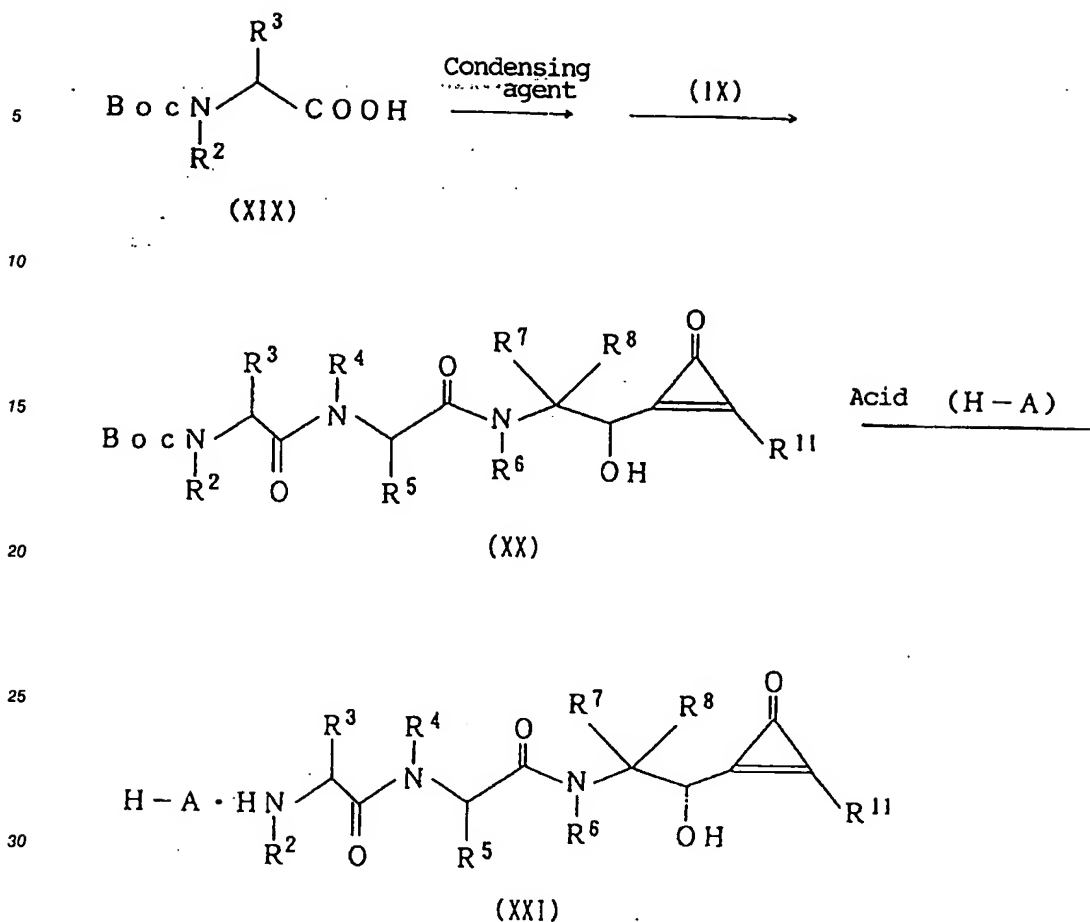
Production 2:



wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are as defined above, and R^{16} is $R^{12}\text{-CO-}$, $R^{12}\text{-O-CO-}$, $R^{12}\text{-NH-CO-}$ or $R^{12}\text{-SO}_2\text{-}$ (in which R^{12} is as defined above).

The cyclopropenone derivative of the general formula (XVIII) above can be prepared by activating carboxyl group of the N-substituted amino acid derivative of formula (XVII) by adding a condensing agent such as isobutyl chloroformate, diphenylphosphoryl azide, carbonyl diimidazole, oxalyl chloride, dicyclohexyl carbodiimide or the like, if necessary, in the presence of an amine such as triethylamine, pyridine or the like and then reacting with amine of formula (XXII) above and a base such as triethylamine, pyridine or the like.

Production 3:



35 wherein R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹¹ and Boc are as defined above.

The N-protected amino acid of the general formula (XIX) above is activated with a condensing agent as described in the Production 1 and then allowed to react a compound (IX) in the presence of a base to give a compound of formula (XX) above. The product (XX) can be converted into an amine salt of formula (XXI) by treating with an acid selected from those described in the Production 1. Similarly, the amino group and hydroxyl group can be converted according to the process described in the Production 1.

As will be seen from the results of Experiments below, the compounds (I) of the invention proved to possess a potent inhibitory activity against thiol protease such as papain, cathepsin B, cathepsin H, cathepsin L, calpain or the like with excellent properties regarding oral absorbance, tissue transference and cell membrane permeability, indicating that they are clinically useful in the treatment of various diseases such as muscular dystrophy, amyotrophy, cardiac infarction, stroke, Alzheimer's disease, conscious disturbance and motor disturbance caused by brain trauma, multiple sclerosis, neuropathy of peripheral nerve, cataract, inflammation, allergy, fulminant hepatitis, osteoporosis, hypercalcemia, breast carcinoma, prostatic carcinoma, prostatomegaly or the like, and can be used as cancer growth inhibitors, cancer metastasis preventive agents or platelet-aggregation inhibitors.

When the compounds (I) of the present invention are clinically applied, they can be administered to subjects to be treated after formulating into appropriate forms containing, as an active ingredient, a therapeutically effective amount of compound (I) together with carriers therefor. The appropriate ratio of the active ingredient to carriers may vary from about 1% by weight to about 90% by weight. For example, the compounds of the present invention may be orally administered after formulating into an appropriate form such as granules, fine granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions or the like. They can be administered intravenously, intramuscularly or subcutaneously in the form of injections. Furthermore, they may be formulated in the form of suppositories, or

powders which are prepared for injections at the time of use.

Formulations of the invention can be prepared using any of known methods in the art employing conventional carriers including organic or inorganic, solid or liquid, pharmaceutical carriers or diluents suitable for oral, enteral or parenteral administration. Examples of excipient usable for preparing solid formulations are lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. Liquid formulations for oral administration such as emulsion, syrups, suspensions, solutions or the like include generally usable inert diluents such as water, vegetable oils or the like. These formulations may further include adjuncts such as humectants, suspension aids, edulcorants, aromatics, tinctures or preservatives in addition to the inert diluents. The compound (I) can be formulated into solutions which are filled in absorbable carriers such as hard or soft gelatin capsules. Examples of solvents and suspending agents usable for preparing pharmaceutical formulations such as injections, suppositories or the like are water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of the base usable for suppositories are cacao butter, emulsified cacao butter, lauric acid, Witte sol and the like.

The dose of compound (I) may vary depending on various factors such as age, conditions or symptoms of the patient to be treated and the like. Appropriate daily dosage of the compound (I) of the present invention on oral administration to adult is generally about 0.01 - 1000 mg though, it is preferable to adjust appropriately for each case according to the conditions as mentioned above. The daily dosage of the compound (I) may be administered once or in two or three divisions at appropriate intervals or intermittently.

Additionally, when the compound (I) is administered in the form of injections, one dosage of 0.001 - 100 mg of said compound can be preferably administered to adult continuously or intermittently.

The following Examples further describe the present invention in more detail, but these are illustrative only and are not intended to limit the scope of the invention.

25 Reference Example 1

Preparation of 2-[(2S)-2-tert-butoxycarbonylamino-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone 2, 2-dimethyl-1,3-propanediyl ketal

To a solution of 3.51 g of 2-phenylcyclopropanone 2, 2-dimethyl-1,3-propanediyl ketal in 30 ml of tetrahydrofuran was added 3.8 g of N,N,N',N'-tetramethylethylenediamine. To the reaction solution chilled at -78 °C was added a 1.55 mol/l solution of n-butyllithium in 10.5 ml of hexane, and the mixture was stirred for 20 minutes. Then, 30 ml of a tetrahydrofuran suspension of anhydrous cerium chloride prepared by drying 8.0 g of cerium chloride heptahydrate at 140 °C/1 mm Hg for 2 hours was added to the mixture, which was stirred for 20 minutes. A solution of 1.82 g of N-tert-butoxycarbonyl-L-valinal in 20 ml of tetrahydrofuran was added, and the resultant mixture was stirred at -78 °C for 2 hours. A solution of 1 ml of water in 5 ml of tetrahydrofuran was added to the reaction mixture, which was allowed to warm at room temperature and filtered through celite. The celite was washed well with ethyl acetate, and the filtrate was dried over sodium sulfate, filtered, concentrated and chromatographed on a column of silica gel, eluting with hexane containing 20% ethyl acetate as a developing solvent to give 2.71 g of the titled product.

Yield: 72%

IR(KBr, cm^{-1}): 3430, 2960, 1855, 1800, 1710, 1690

NMR(CD_3OD , δ): 0.95-1.60(m, 12H), 1.38(s, 3H), 1.42(s, 6H), 1.95-2.15(m, 1H), 3.60-3.75(m, 1H), 3.75-3.95(m, 4H), 5.0-5.10(m, 1H), 6.03(d, J=10Hz, 0.33H), 6.23(d, J=10Hz, 0.67H), 7.40-7.65(m, 3H), 7.70-7.90(m, 2H)

Reference Example 2

Preparation of 2-[(2S)-2-amino-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone hydrochloride

To 8 ml of a dioxane solution of 3.12 g of 2-[(2S)-2-tert-butoxycarbonylamino-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone 2,2-dimethyl-1,3-propanediyl ketal obtained in Reference Example 1 were added 0.2 ml of water and 24 ml of a dioxane solution of 4 N hydrogen chloride, and the mixture was stirred for 20 minutes. The resulting crystals were filtered and washed with dioxane to give 1.87 g of the titled product.

Yield: 94%

IR(KBr, cm^{-1}): 3200, 1855, 1618

NMR(CD_3OD , δ): 1.21(t, J=7Hz, 4.5H), 1.24(t, J=7Hz, 1.5H), 2.0-2.2(m, 0.25H), 2.2-2.4(m, 0.75H), 3.38(t, J=6Hz, 0.25H), 3.45(t, J=6Hz, 0.75H), 5.21(d, J=6Hz, 0.75H), 5.45(d, J=6Hz, 0.25H), 7.60-7.80(m, 3H),

8.10-8.20(m, 2H)

Example 1

- 5 Preparation of 2-[(1S,2S)-2-{(S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino}-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (Comp. No. 77 in Table 1)

To a solution of 2.46 g of N-cyclohexylmethoxycarbonyl-(S)-leucine in 40 ml of methylene chloride chilled at -5°C were added 0.92 g of triethylamine and 1.15 g of isobutyl chloroformate, and the resultant
 10 mixture was stirred for 15 minutes. Further, 1.87 g of 2-[(2S)-2-amino-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone hydrochloride prepared in Reference Example 2 and 0.97 g of triethylamine were added, and one hour later 10 ml of 0.5 N hydrochloric acid was added. The resultant mixture was shaken with methylene chloride, and the organic layer was washed with water, saturated aqueous sodium bicarbonate and saturated brine in that order, dried over magnesium sulfate and filtered. The filtrate was concentrated
 15 and chromatographed on a column of silica gel, eluting with hexane:ethyl acetate (1:1) as developing solvent, and the product was recrystallized from diethyl ether to give 1.86 g of the titled product.

Yield: 55%

mp: 85-89°C

IR(KBr, cm⁻¹): 3330, 1858, 1695, 1658, 1625

20 NMR(CDCl₃, δ): 0.65-1.80(m, 26H), 2.25-2.45(m, 1H), 3.55-3.85(m, 3H), 4.0-4.15(m, 1H), 5.12(d, J=4Hz, 1H), 5.30-5.45(m, 1H), 7.40-7.65(m, 4H), 7.95-8.05(m, 2H)

Example 2

- 25 Preparation of 2-[(1R, 2S)-2-{(S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino}-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (Comp. No. 77 in Table 1)

The titled isomer was obtained as a product of the chromatography on a column of silica gel in Example 1.

30 Yield: 18%

mp: 148-149°C

IR(KBr, cm⁻¹): 3350, 3260, 1860, 1825, 1715, 1653, 1625

NMR(CDCl₃, δ): 0.60-1.80(m, 26H), 2.05-2.25(m, 1H), 3.60-3.85(m, 2H), 4.05-4.20(m, 2H), 5.15(d, J=3Hz, 1H), 5.20-5.40(m, 1H), 7.05(d, J=8Hz, 1H), 7.45-7.60(m, 3H), 7.95-8.05(m, 2H)

Example 3

Preparation of 2-[(1R,2S)-1-acetoxy-2-{(S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino}-3-methylbutyl]-3-phenylcyclopropanone (Comp. No. 78 in Table 1)

40 To 5 ml of a methylene chloride solution of 149 mg of 2-[(1R,2S)-2-{(S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino}-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone obtained in Example 2 were added 81 mg of acetyl chloride and 102 mg of triethylamine. The resultant mixture was stirred at room temperature for 3 hours, mixed with diluted hydrochloric acid and shaken with methylene chloride. The organic layer was washed with water, saturated aqueous sodium bicarbonate and saturated brine in that order, dried over magnesium sulfate and filtered. The filtrate was concentrated and chromatographed on a column of silica gel, eluting with hexane:ethyl acetate (1:1) to give 73 mg of the titled product.

Yield: 45%

50 IR(KBr, cm⁻¹): 3350, 3280, 1868, 1758, 1720, 1704, 1670, 1635

NMR(CDCl₃, δ): 0.79(d, J=7.0Hz, 3H), 0.81(d, J=6.3Hz, 3H), 0.70-0.95(m, 2H), 1.02(d, J=6.6Hz, 3H), 1.15-(d, J=6.6Hz, 3H), 1.05-1.35(m, 4H), 1.35-1.85(m, 8H), 2.03(m, 1H), 2.20(s, 3H), 3.75(s, 2H), 4.10(m, 1H), 4.31(m, 1H), 5.06(d, J=8.0Hz, 1H), 6.12(d, J=4.2Hz, 1H), 6.52(d, J=8.1Hz, 1H), 7.45-7.65(m, 3H), 7.84(d, J=7.1Hz, 2H)

55 The compounds in the following Examples 4 - 120 were prepared by the same manner as in Reference Examples 1 - 2 and Examples 1, 2 and 3. Physicochemical properties of each compound are shown below.

Example 4

Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]cyclopropanone (compd. No. 4 in Table 1)

IR(KBr, cm^{-1}): 3310, 1825, 1690, 1650

5 NMR(CDCl_3 , δ): 0.80-1.80(m, 26H), 1.90-2.35(m, 2H), 3.60-4.25(m, 4H), 4.87-5.05(m, 1H), 5.05-5.45(m, 1H), 6.85-7.03(m, 0.3H), 7.35-7.52(m, 0.7H), 8.54(s, 0.7H), 8.62(s, 0.3H)

Example 5

10 Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-4-methylpentyl]-cyclopropanone (compd. No. 10 in Table 1)

IR(KBr, cm^{-1}): 3320, 1825, 1697, 1652

15 NMR(CDCl_3 , δ): 0.90-1.05(m, 12H), 1.40-1.80(m, 6H), 4.05-4.32(m, 2H), 4.68-4.87(m, 1H), 5.09(s, 2H), 4.90-5.60(m, 2H), 6.85-7.10(m, 1H), 7.34(s, 5H), 8.43(s, 0.95H), 8.62(s, 0.05H)

Example 6

20 Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-cyclopropanone (compd. No. 15 in Table 1)

IR(KBr, cm^{-1}): 3340, 1830, 1690, 1650

25 NMR(CDCl_3 , δ): 0.80-1.05(m, 11H), 1.10-1.88(m, 18H), 2.24(s, 1H), 3.73-3.95(m, 2H), 4.05-4.30(m, 2H), 4.80-4.93(m, 1H), 5.20-5.35(m, 0.2H), 5.35-5.55(m, 0.8H), 5.55-5.75(m, 0.8H), 6.95-7.05(m, 0.2H), 8.57(s, 0.8H), 8.68(s, 0.2H)

Example 7

30 Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-cyclopropanone (compd. No. 16 in Table 1)

IR(KBr, cm^{-1}): 3320, 1828, 1690, 1645

35 NMR(CDCl_3 , δ): 0.75-1.0(m, 9H), 1.15-1.85(m, 9H), 2.25(s, 1H), 3.98-4.27(m, 2H), 4.68-4.87(m, 1H), 5.07(s, 2H), 5.45-5.80(m, 1.8H), 6.95-7.05(m, 0.2H), 7.32(s, 5H), 8.43(s, 0.8H), 8.57(s, 0.2H)

Example 8

40 Preparation of 2-[(2S)-1-acetoxy-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)hexyl]-cyclopropanone (compd. No. 20 in Table 1)

IR(neat, cm^{-1}): 3320, 1845, 1755, 1725, 1710, 1668

45 NMR(CDCl_3 , δ): 0.80-1.0(m, 9H), 1.20-1.75(m, 9H), 2.15(s, 0.45H), 2.20(s, 2.55H), 4.08-4.23(m, 1H), 4.35-4.50(m, 1H), 5.20(s, 2H), 5.18(d, $J=7\text{Hz}$, 0.85H), 5.22(d, $J=7\text{Hz}$, 0.15H), 5.70(d, $J=4\text{Hz}$, 0.85H), 6.78(d, $J=4\text{Hz}$, 0.15H), 6.43(d, $J=8\text{Hz}$, 0.15H), 6.46(d, $J=8\text{Hz}$, 0.85H), 7.35(s, 5H), 8.49(s, 0.85H), 8.52(s, 0.15H)

Example 9

50 Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-phenylpropyl]-cyclopropanone (compd. No. 26 in Table 1)

IR(KBr, cm^{-1}): 3330, 1830, 1700, 1655

55 NMR(CDCl_3 , δ): 0.65-0.95(m, 6H), 1.10-1.65(m, 3H), 1.93(s, 1H), 2.75-3.25(m, 2H), 3.90-4.55(m, 2H), 4.60-4.83(m, 1H), 5.05(s, 2H), 5.15-5.85(m, 2H), 7.05-7.45(m, 10H), 8.39(s, 0.8H), 8.53(s, 0.2H)

Example 10

Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-methylcyclopropanone (compd. No. 34 in Table 1)

IR(KBr, cm^{-1}): 3320, 1845, 1690, 1653, 1630 NMR(CDCl_3 , δ): 0.85-1.10(m, 11H), 1.10-1.95(m, 18H), 2.33(s, 3H), 2.49(s, 1H), 3.75-3.97(m, 2H), 3.97-4.28(m, 2H), 4.73-4.90(m, 1H), 5.20-5.85(m, 1.6H), 7.10-7.50(m, 0.4H)

5 Example 11

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-4-methylpentyl]-3-ethylcyclopropanone (compd. No. 40 in Table 1)

10 IR(neat, cm^{-1}): 3330, 1845, 1700, 1658, 1625
NMR(CDCl_3 , δ): 0.85-1.05(m, 12H), 1.30(q, $J=7\text{Hz}$, 3H), 1.40-1.75(m, 6H), 1.83(s, 1H), 2.58-2.78(m, 2H), 3.80-4.30(m, 2H), 4.65-4.85(m, 1H), 4.90-5.03(m, 0.5H), 5.09(m, 2H), 5.37-5.65(m, 1.5H), 5.70-5.85(m, 0.5H), 7.05-7.25(m, 0.5H), 7.34(s, 5H)

15 Example 12

Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-isopentylcyclopropanone (compd. No. 44 in Table 1)

20 IR(KBr, cm^{-1}): 3310, 1838, 1720, 1698, 1652, 1620
NMR(CDCl_3 , δ): 0.85-1.10(m, 17H), 1.10-1.85(m, 21H), 2.45-2.55(m, 1H), 2.55-2.70(m, 2H), 3.73-3.93(m, 2H), 3.93-4.25(m, 2H), 4.70-4.85(m, 1H), 5.25-5.85(m, 1.6H), 7.30-7.45(m, 0.4H)

Example 13

25 Preparation of 2-[(1S,2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-((Z)-1-hexenyl)cyclopropanone (compd. No. 55 in Table 1)
mp: 138-140 °C

IR(KBr, cm^{-1}): 3290, 1838, 1711, 1655, 1630
30 NMR(CDCl_3 , δ): 0.83-1.08(m, 14H), 1.10-2.05(m, 22H), 2.56(m, 2H), 3.85(s, 2H), 4.02(m, 1H), 4.15(m, 1H), 4.82(m, 1H), 5.22-5.48(m, 2H), 6.26(d, $J=10\text{Hz}$, 1H), 6.48(m, 1H), 7.08(m, 1H)

Example 14

35 Preparation of 2-[(1S,2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-((Z)-1-hexenyl)cyclopropanone (compd. No. 56 in Table 1)

mp: 87-94 °C

IR(KBr, cm^{-1}): 3300, 1836, 1689, 1645
40 NMR(CDCl_3 , δ): 0.80-1.03(m, 12H), 1.22-1.80(m, 13H), 2.56(m, 2H), 4.01(m, 1H), 4.17(m, 1H), 4.77(m, 1H), 5.08(s, 2H), 5.19(m, 1H), 5.45(m, 1H), 6.24(d, $J=9.9\text{Hz}$, 1H), 6.46(m, 1H), 7.04(d, $J=7.7\text{Hz}$, 1H), 7.33(s, 5H)

Example 15

45 Preparation of 2-[(1S,2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-((E)-1-hexenyl)cyclopropanone (compd. No. 58 in Table 1)

mp: 116 °C

IR(KBr, cm^{-1}): 3308, 1842, 1698, 1655
50 NMR(CDCl_3 , δ): 0.85-1.0(m, 12H), 1.15-1.90(m, 13H), 2.27(dt, $J=6.8\text{Hz}$, 6.5Hz, 2H), 3.97(m, 1H), 4.17(m, 1H), 4.75(m, 1H), 5.08(s, 2H), 5.57(d, $J=6.5\text{Hz}$, 1H), 6.24(d, $J=16\text{Hz}$, 1H), 6.90(dt, $J=16\text{Hz}$, 6.8Hz, 1H), 7.10(d, $J=6.8\text{Hz}$, 1H), 7.32(s, 5H)

Example 16

55 Preparation of 2-[(1S,2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 68 in Table 1)

mp: 156-158 °C

IR(KBr, cm⁻¹): 3290, 1850, 1690, 1643, 1618

NMR(CDCl₃, δ): 0.98(d, J = 5.9Hz, 3H), 1.07(d, J = 6.6Hz, 3H), 1.19(d, J = 7.0Hz, 3H), 2.36(m, 1H), 3.61(m, 1H), 4.18(m, 1H), 4.90-5.15(m, 3H), 5.47(m, 1H), 7.31(s, 5H), 7.25-7.65(m, 5H), 7.95(d, J = 7.4Hz, 2H)

5

Example 17

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-3-methylbutyl)-3-phenylcyclopropenone (compd. No. 68 in Table 1)

10

IR(KBr, cm⁻¹): 3280, 1852, 1696, 1642, 1618

NMR(CDCl₃, δ): 0.85-1.30(m, 9H), 2.11(m, 0.4H), 2.34(m, 0.6H), 3.64(m, 0.6H), 4.02-4.28(m, 1.4H), 4.85-5.20(m, 3H), 5.49(m, 0.4H), 5.62(m, 0.6H), 6.99(d, J = 7.7Hz, 0.6H), 7.15-7.38(m, 5.4H), 7.15-7.65(m, 4H), 7.88-8.05(m, 2H)

15

Example 18

Preparation of 2-[(1S, 2S)-2-((S)-2-benzyloxycarbonylamino-3-methylbutyl)-3-phenylcyclopropenone (compd. No. 70 in Table 1)

20

mp: 157-158 °C

IR(KBr, cm⁻¹): 3310, 1850, 1697, 1643, 1618

NMR(CDCl₃, δ): 0.74(d, J = 6.8Hz, 3H), 0.85(d, J = 6.7Hz, 3H), 0.98(d, J = 6.5Hz, 3H), 1.08(d, J = 6.6Hz, 3H), 2.04(m, 1H), 2.36(m, 1H), 3.69(m, 1H), 4.01(m, 1H), 4.90-5.10(m, 3H), 5.47(d, J = 8.2Hz, 1H), 6.15(d, J = 8.2Hz, 1H), 7.30(s, 5H), 7.40-7.60(m, 4H), 7.93-8.0(m, 2H)

25

Example 19

Preparation of 2-[(1R, 2S)-2-((S)-2-benzyloxycarbonylamino-3-methylbutyl)-3-phenylcyclopropenone (compd. No. 70 in Table 1)

30

mp: 63-71 °C

IR(KBr, cm⁻¹): 3310, 1860, 1700, 1660, 1630

NMR(CDCl₃, δ): 0.79(d, J = 6.8Hz, 3H), 0.80(d, J = 6.9Hz, 3H), 1.05(d, J = 6.7Hz, 3H), 1.13(d, J = 6.6Hz, 3H), 1.98(m, 1H), 2.14(m, 1H), 3.90-4.15(m, 2H), 4.92(d, J = 12Hz, 1H), 5.03(d, J = 12Hz, 1H), 5.13(m, 1H), 5.42(d, J = 7.0Hz, 1H), 6.96(d, J = 7.2Hz, 1H), 7.30(s, 5H), 7.40-7.63(m, 4H), 7.97(d, J = 7.0Hz, 2H)

35

Example 20

Preparation of 2-[(1S, 2S)-1-hydroxy-2-((S)-2-isobutoxycarbonylamino-4-methylvaleryl)-3-phenylcyclopropenone (compd. No. 72 in Table 1)

40

mp: 145-146 °C

IR(KBr, cm⁻¹): 3320, 1848, 1692, 1644, 1620

NMR(CDCl₃, δ): 0.77(d, J = 4.3Hz, 6H), 0.87(d, J = 6.7Hz, 6H), 1.01(d, J = 6.5Hz, 3H), 1.09(d, J = 6.5Hz, 3H), 1.29(m, 2H), 1.52(m, 1H), 1.84(m, 1H), 2.39(m, 1H), 3.60-3.87(m, 3H), 4.10(m, 1H), 5.12(d, J = 3.5Hz, 1H), 5.29(m, 1H), 6.20(s, 1H), 7.38-7.60(m, 4H), 7.98(d, J = 6.9Hz, 2H)

45

Example 21

Preparation of 2-[(1R, 2S)-1-hydroxy-2-((S)-2-isobutoxycarbonylamino-4-methylvaleryl)-3-phenylcyclopropenone (compd. No. 72 in Table 1)

50

mp: 173-174 °C

IR(KBr, cm⁻¹): 3400, 3260, 1863, 1828, 1722, 1655, 1626

NMR(CDCl₃, δ): 0.71(d, J = 4.1Hz, 6H), 0.84(d, J = 6.6Hz, 6H), 1.08(d, J = 6.5Hz, 3H), 1.14(d, J = 6.6Hz, 3H), 1.30-1.60(m, 2H), 1.60-1.90(m, 2H), 2.13(m, 1H), 3.55-3.90(m, 2H), 3.98-4.18(m, 2H), 5.03-5.18(m, 3H), 6.79(m, 1H), 7.40-7.63(m, 3H), 7.99(d, J = 7.8Hz, 2H)

55

Example 22

Preparation of 2-[(1S, 2S)-2-((S)-2-tert-butoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 73 in Table 1)

5

mp: 158-161 °C

IR(KBr, cm⁻¹): 3330, 1858, 1685, 1655, 1625

NMR(CDCl₃, δ): 0.75(d, J = 6.4Hz, 6H), 1.02(d, J = 6.7Hz, 3H), 1.09(d, J = 6.6Hz, 3H), 1.17-1.60(m, 3H), 1.39-
(s, 9H), 2.39(m, 1H), 3.65(m, 1H), 4.04(m, 1H), 5.02-5.18(m, 2H), 6.25(m, 1H), 7.33(m, 1H), 7.45-7.60(m, 3H),
7.95-8.05(m, 2H)

10

Example 23

Preparation of 2-[(1R, 2S)-2-((S)-2-tert-butoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 73 in Table 1)

15

mp: 182-183 °C

IR(KBr, cm⁻¹): 3380, 3260, 1860, 1825, 1708, 1655, 1625

NMR(CDCl₃, δ): 0.68(d, J = 5.6Hz, 6H), 1.08(d, J = 6.6Hz, 3H), 1.11(d, J = 6.7Hz, 3H), 1.25-1.55(m, 3H), 1.38-
(s, 9H), 2.13(m, 1H), 3.98-4.13(m, 2H), 5.04(d, J = 5.9Hz, 1H), 5.13(dd, J = 6.4Hz, 3.0Hz, 1H), 5.35(d,
J = 6.4Hz, 1H), 8.95(d, J = 7.0Hz, 1H), 7.45-7.65(m, 3H), 7.98-8.07(m, 2H)

20

Example 24

Preparation of 2-[(1S, 2S)-2-{N-((S)-2-cyclohexylcarbonylamino-4-methylvaleryl)-N-methylamino}-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 80 in Table 1)

25

IR(KBr, cm⁻¹): 3416, 1856, 1716, 1640

NMR(CDCl₃, δ): 0.86(d, J = 7.1Hz, 3H), 0.92(d, J = 7.1Hz, 3H), 0.97(d, J = 6.5Hz, 3H), 1.10(d, J = 6.6Hz, 3H),
0.65-1.80(m, 14H), 2.64(m, 1H), 3.22(s, 3H), 3.05-3.40(m, 2H), 3.53(dd, J = 11Hz, 7.0Hz, 1H), 4.45(m, 1H),
4.87(d, J = 8.7Hz, 1H), 5.10(dd, J = 9.1Hz, 4.3Hz, 1H), 6.80(m, 1H), 7.35-7.60(m, 3H), 7.93(d, J = 7.2Hz, 2H)

30

Example 25

Preparation of 2-[(1S, 2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 83 in Table 1)

35

mp: 84-94 °C

IR(KBr, cm⁻¹): 3320, 1855, 1700, 1655, 1625

NMR(CDCl₃, δ): 0.60-0.85(m, 6H), 0.97(d, J = 6Hz, 3H), 1.07(d, J = 6Hz, 3H), 1.20-1.60(m, 3H), 1.85-2.25(m,
1H), 2.25-2.45(m, 1H), 3.55-3.70(m, 1H), 4.0-4.10(m, 1H), 4.85-5.15(m, 3H), 5.53(d, J = 8Hz, 1H), 7.29(s, 5H),
7.40-7.60(m, 4H), 7.90-8.05(m, 2H)

40

Example 26

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 83 in Table 1)

45

IR(KBr, cm⁻¹): 3300, 1855, 1700, 1655, 1625

NMR(CDCl₃, δ): 0.60-1.55(m, 15H), 2.05-2.25(m, 1.6H), 2.25-2.45(m, 0.4H), 3.55-3.70(m, 0.4H), 3.95-4.25(m,
1.6H), 4.85-5.20(m, 3H), 5.53(d, J = 8Hz, 0.6H), 5.62(d, J = 8Hz, 0.4H), 7.08(d, J = 8Hz, 0.6H), 7.50(s, 5H),
7.40-7.65(m, 3.4H), 7.90-8.10(m, 2H)

50

Example 27

Preparation of 2-[(1S, 2S)-2-((S)-2-(N-benzyloxycarbonyl-N-methylamino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 85 in Table 1)

55

mp: 117 °C

IR(KBr, cm^{-1}): 3335, 3298, 1858, 1699, 1672, 1628

NMR(CDCl_3 , δ): 0.70-0.90(m, 6H), 0.96(d, $J=6.6\text{Hz}$, 3H), 1.03(d, $J=6.6\text{Hz}$, 3H), 1.25-1.65(m, 3H), 2.35(m, 1H), 2.57(s, 3H), 3.62(m, 1H), 4.64(m, 1H), 5.07(d, $J=4.9\text{Hz}$, 1H), 5.15(s, 2H), 7.04(d, $J=7.5\text{Hz}$, 1H), 7.36(s, 5H), 7.38-7.58(m, 3H), 7.94(d, $J=6.5\text{Hz}$, 2H)

Example 28

Preparation of 2-[(1R, 2S)-2-[(S)-2-(N-benzyloxycarbonyl-N-methylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 85 in Table 1)

mp: 112 °C

IR(KBr, cm^{-1}): 3320, 3283, 1863, 1703, 1661, 1632

NMR(CDCl_3 , δ): 0.70(d, $J=8.4\text{Hz}$, 3H), 0.73(d, $J=6.7\text{Hz}$, 3H), 0.96(d, $J=5.1\text{Hz}$, 3H), 1.09(d, $J=6.4\text{Hz}$, 3H), 1.28(m, 1H), 1.40-1.70(m, 2H), 2.05(m, 1H), 2.80(s, 3H), 3.94(m, 1H), 4.48(t, $J=7.3\text{Hz}$, 1H), 4.94-5.20(m, 3H), 6.65(m, 1H), 7.33(s, 5H), 7.38-7.62(m, 3H), 7.98(d, $J=6.4\text{Hz}$, 2H)

Example 29

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-pyridylmethoxycarbonylamino)-valeryl-amino]butyl]-3-phenylcyclopropanone hydrochloride (compd. No. 97 in Table 1)

mp: 158-160 °C(dec.)

IR(KBr, cm^{-1}): 3279, 1854, 1738, 1676, 1630, 1615

NMR(CD_3OD , δ): 0.52(d, $J=6.6\text{Hz}$, 3H), 0.64(d, $J=6.5\text{Hz}$, 3H), 0.90(d, $J=6.7\text{Hz}$, 3H), 0.95-1.33(m, 2H), 1.07(d, $J=6.7\text{Hz}$, 3H), 1.46(m, 1H), 2.05(m, 1H), 3.97-4.16(m, 2H), 5.21(d, $J=2.4\text{Hz}$, 1H), 5.28(d, $J=15\text{Hz}$, 1H), 5.43(d, $J=15\text{Hz}$, 1H), 7.50-7.70(m, 3H), 7.97-8.15(m, 4H), 8.61(td, $J=8.0\text{Hz}$, 1.5Hz, 1H), 8.81(d, $J=5.2\text{Hz}$, 1H)

Example 30

Preparation of 2-[(1R, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-pyridylmethoxycarbonylamino)-valeryl-amino]butyl]-3-phenylcyclopropanone (compd. No. 97 in Table 1)

mp: 52-59 °C

IR(KBr, cm^{-1}): 3300, 1858, 1715, 1660, 1630

NMR(CDCl_3 , δ): 0.71(d, $J=7.4\text{Hz}$, 6H), 1.03(d, $J=6.3\text{Hz}$, 3H), 1.11(d, $J=6.4\text{Hz}$, 3H), 1.38-1.65(m, 3H), 2.42-(m, 1H), 4.09(m, 1H), 4.20(m, 1H), 4.95-5.28(m, 3H), 5.43(m, 1H), 5.78(d, $J=7.7\text{Hz}$, 1H), 7.15-7.38(m, 3H), 7.38-7.62(m, 3H), 7.62-7.78(m, 1H), 7.97(d, $J=7.0\text{Hz}$, 2H), 8.54(s, 1H)

Example 31

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(4-pyridylmethoxycarbonylamino)-valeryl-amino]butyl]-3-phenylcyclopropanone hydrochloride (compd. No. 99 in Table 1)

mp: 122-129 °C(dec.)

IR(KBr, cm^{-1}): 3260, 1858, 1720, 1650, 1640, 1615

NMR(CD_3OD , δ): 0.53(d, $J=6.6\text{Hz}$, 3H), 0.64(d, $J=6.5\text{Hz}$, 3H), 0.91(d, $J=6.7\text{Hz}$, 3H), 1.08(d, $J=6.7\text{Hz}$, 3H), 0.79-1.20(m, 2H), 1.53(m, 1H), 2.10(m, 1H), 4.0-4.18(m, 2H), 5.21(s, 1H), 5.24(d, $J=20\text{Hz}$, 1H), 5.30(d, $J=20\text{Hz}$, 1H), 7.53-7.70(m, 3H), 7.95-8.15(m, 4H), 8.82(d, $J=6.8\text{Hz}$, 2H)

Example 32

Preparation of 2-[(1R, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(4-pyridylmethoxycarbonylamino)-valeryl-amino]butyl]-3-phenylcyclopropanone hydrochloride (compd. No. 99 in Table 1)

mp: 116-134 °C(dec.)

IR(KBr, cm^{-1}): 3260, 1857, 1720, 1660, 1635, 1620

NMR(CD₃OD, δ): 0.82(d, J=6.3Hz, 6H), 0.84(d, J=6.4Hz, 6H), 1.53(m, 2H), 1.73(m, 1H), 2.13(m, 1H), 4.0-4.25(m, 2H), 5.05(d, J=7.0Hz, 1H), 5.32(d, J=17Hz, 1H), 5.43(d, J=17Hz, 1H), 7.53-7.70(m, 3H), 7.90-8.10(m, 4H), 8.82(d, J=6.8Hz, 2H)

5 Example 33

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenoxy-carbonylamino)valeryl-amino]-3-phenylcyclopropanone (compd. No. 102 in Table 1)

10 mp: 105-115 °C

IR(KBr, cm⁻¹): 3304, 1856, 1717, 1657, 1626

NMR(CDCl₃, δ): 0.75(d, J=6.1Hz, 3H), 0.77(d, J=6.3Hz, 3H), 1.0(d, J=6.6Hz, 3H), 1.04(d, J=6.7Hz, 3H), 1.35(m, 2H), 1.56(m, 1H), 2.33(m, 1H), 3.70(m, 1H), 4.17(m, 1H), 5.09(dd, J=8.3Hz, 4.1Hz, 1H), 6.17(d, J=9.1Hz, 1H), 6.21(d, J=8.3Hz, 1H), 7.02(d, J=7.7Hz, 2H), 7.16(t, J=7.2Hz, 1H), 7.30(t, J=7.4Hz, 2H),
15 7.42-7.62(m, 3H), 7.70(d, J=7.9Hz, 1H), 7.94(d, J=6.7Hz, 2H)

Example 34

20 Preparation of 2-[(1S, 2S)-2-((S)-2-amino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone hydrochloride (compd. No. 105 in Table 1)

mp: 147-153 °C(dec.)

IR(KBr, cm⁻¹): 3260, 1858, 1675, 1616

NMR(CD₃OD, δ): 0.47(d, J=6.5Hz, 3H), 0.71(d, J=6.5Hz, 3H), 1.02(d, J=6.7Hz, 3H), 1.12(d, J=6.7Hz, 3H),
25 1.20(m, 2H), 1.42(m, 1H), 2.10(m, 1H), 3.81(dd, J=8.9Hz, 6.1Hz, 1H), 4.11(dd, J=9.7Hz, 2.2Hz, 1H), 5.23(d, J=2.2Hz, 1H), 7.55-7.70(m, 3H), 8.03-8.13(m, 2H)

Example 35

30 Preparation of 2-[(1R, 2S)-2-((S)-2-amino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone hydrochloride (compd. No. 105 in Table 1)

mp: 133-136 °C

IR(KBr, cm⁻¹): 3260, 1860, 1675, 1620

NMR(CD₃OD, δ): 0.82(d, J=5.6Hz, 3H), 0.85(d, J=5.7Hz, 3H), 1.04(d, J=6.7Hz, 3H), 1.10(d, J=6.8Hz, 3H),
35 1.58-1.80(m, 3H), 2.16(m, 1H), 3.84(m, 1H), 4.03(t, J=7.0Hz, 1H), 5.18(d, J=6.6Hz, 1H), 7.55-7.70(m, 3H), 8.07(d, J=6.9Hz, 2H)

Example 36

40

Preparation of 2-[(1S, 2S)-2-((S)-2-acetyl-amino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 106 in Table 1)

mp: 94-105 °C

45 IR(KBr, cm⁻¹): 3280, 1858, 1645-1620

NMR(CDCl₃, δ): 0.73(d, J=6.3Hz, 6H), 0.99(d, J=7.1Hz, 3H), 1.09(d, J=7.0Hz, 3H), 1.27-1.55(m, 3H), 2.03(s, 3H), 2.28(m, 1H), 3.79(m, 1H), 4.39(m, 1H), 5.14(d, J=3.3Hz, 1H), 6.22(m, 1H), 6.69(d, J=8.3Hz, 1H), 7.45-7.60(m, 3H), 7.72(d, J=8.6Hz, 1H), 7.97(dd, J=8.0Hz, 1.5Hz, 2H)

50 Example 37

Preparation of 2-[(1S, 2S)-1-hydroxy-2-((S)-2-isohexanoyl-amino-4-methylvaleryl-amino)-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 114 in Table 1)

55 mp: 148-151 °C

IR(KBr, cm⁻¹): 3293, 1856, 1640

NMR(CDCl₃, δ): 0.73(d, J=5.9Hz, 3H), 0.74(d, J=6.0Hz, 3H), 0.85(d, J=6.2Hz, 6H), 0.98(d, J=6.7Hz, 3H), 1.08(d, J=6.6Hz, 3H), 1.30-1.60(m, 6H), 2.11(t, J=6.7Hz, 2H), 2.27(m, 1H), 3.83(m, 1H), 4.43(m, 1H), 5.13-

(dd, J=7.9Hz, 4.2Hz, 1H), 6.16(d, J=7.9Hz, 1H), 6.53(d, J=7.9Hz, 1H), 7.45-7.55(m, 3H), 7.62(d, J=8.3Hz, 1H), 7.98(dd, J=7.7Hz, 1.4Hz, 2H)

Example 38

5

Preparation of 2-[(1S, 2S)-1-hydroxy-2-((S)-2-lauroylamino-4-methylvaleryl-amino)-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 120 in Table 1)

mp: 123-127 °C

10

IR(KBr, cm⁻¹): 3293, 1856, 1640

NMR(CDCl₃, δ): 0.71(d, J=5.9Hz, 3H), 0.73(d, J=5.9Hz, 3H), 0.87(t, J=6.2Hz, 3H), 0.97(d, J=6.6Hz, 3H), 1.08(d, J=6.6Hz, 3H), 1.15-1.45(m, 16H), 1.45-1.80(m, 5H), 2.10(t, J=7.6Hz, 2H), 2.24(m, 1H), 3.84(m, 1H), 4.42(m, 1H), 5.13(dd, J=7.9Hz, 3.9Hz, 1H), 6.22(d, J=8.3Hz, 1H), 6.64(d, J=7.9Hz, 1H), 7.42-7.60(m, 3H), 7.67(d, J=8.3Hz, 1H), 7.98(dd, J=8.0Hz, 1.7Hz, 2H)

15

Example 39

Preparation of 2-[(1S, 2S)-2-((S)-2-{(3-cyclohexylpropionylamino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 124 in Table 1)

20

mp: 126-128 °C

IR(KBr, cm⁻¹): 3300, 1858, 1640

NMR(CDCl₃, δ): 0.74(d, J=6.3Hz, 3H), 0.75(d, J=6.3Hz, 3H), 0.70-0.95(m, 2H), 0.98(d, J=7.0Hz, 3H), 1.08(d, J=7.0Hz, 3H), 1.05-1.35(m, 4H), 1.35-1.55(m, 5H), 1.55-1.75(m, 5H), 2.11(t, J=8.7Hz, 2H), 2.27(m, 1H), 3.80(m, 1H), 4.41(m, 1H), 5.13(m, 1H), 6.11(s, 1H), 6.42(d, J=8.5Hz, 1H), 7.45-7.65(m, 4H), 7.99(dd, J=8.0Hz, 1.4Hz, 2H)

25

Example 40

Preparation of 2-[(1S, 2S)-2-((S)-2-cyclohexylcarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 129 in Table 1)

mp: 116-120 °C

IR(KBr, cm⁻¹): 3297, 1856, 1640

NMR(CDCl₃, δ): 0.72(d, J=5.4Hz, 3H), 0.74(d, J=4.2Hz, 3H), 0.97(d, J=6.6Hz, 3H), 1.07(d, J=6.6Hz, 3H), 0.95-1.55(m, 8H), 1.55-1.80(m, 5H), 2.05(m, 1H), 2.24(m, 1H), 3.83(m, 1H), 4.39(m, 1H), 5.13(dd, J=7.8Hz, 4.1Hz, 1H), 6.21(d, J=8.0Hz, 1H), 6.46(d, J=7.8Hz, 1H), 7.38-7.55(m, 3H), 7.62(d, J=8.5Hz, 1H), 7.98(dd, J=7.8Hz, 1.5Hz, 2H)

Example 41

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenylacetylaminovaleryl-amino)butyl]-3-phenylcyclopropanone (compd. No. 132 in Table 1)

mp: 152-154 °C

IR(KBr, cm⁻¹): 3280, 1856, 1635

NMR(CDCl₃, δ): 0.68(d, J=5.5Hz, 6H), 0.91(d, J=6.7Hz, 3H), 1.03(d, J=6.6Hz, 3H), 1.18-1.43(m, 3H), 2.23(m, 1H), 3.39(d, J=15Hz, 1H), 3.47(d, J=15Hz, 1H), 3.72(m, 1H), 4.38(m, 1H), 5.07(m, 1H), 6.03(m, 1H), 6.37(d, J=7.8Hz, 1H), 7.08-7.19(m, 2H), 7.19-7.30(m, 3H), 7.40-7.60(m, 4H), 7.96(dd, J=7.7Hz, 1.2Hz, 2H)

50

Example 42

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-(3-phenylpropionylamino)-valeryl-amino)butyl]-3-phenylcyclopropanone (compd. No. 133 in Table 1)

55

mp: 148 °C

IR(KBr, cm⁻¹): 3287, 1854, 1640

NMR(CDCl₃, δ): 0.67(d, J=3.9Hz, 6H), 0.95(d, J=6.8Hz, 3H), 1.06(d, J=6.8Hz, 3H), 1.18-1.40(m, 3H), 2.27-

(m, 1H), 2.43(t, J=7.9Hz, 2H), 3.70-3.90(m, 2H), 3.74(m, 1H), 4.39(m, 1H), 5.09(m, 1H), 6.19(d, J=8.3Hz, 1H), 6.59(d, J=8.2Hz, 1H), 7.07-7.30(m, 5H), 7.40-7.60(m, 4H), 7.96(dd, J=6.6Hz, 1.7Hz, 2H)

Example 43

5

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(4-phenylbutyrylamino)valerylamino]butyl]-3-phenylcyclopropanone (compd. No. 134 in Table 1)

mp: 91-96 °C

10

IR(KBr, cm⁻¹): 3293, 1856, 1640

NMR(CDCl₃, δ): 0.72(d, J=5.1Hz, 6H), 0.97(d, J=6.6Hz, 3H), 1.06(d, J=6.5Hz, 3H), 1.25-1.55(m, 3H), 1.84-(m, 2H), 2.11(m, 2H), 2.27(m, 1H), 2.55(t, J=7.5Hz, 2H), 3.80(m, 1H), 4.42(m, 1H), 5.10(m, 1H), 6.19(d, J=8.1Hz, 1H), 6.62(d, J=7.7Hz, 1H), 7.05-7.35(m, 5H), 7.40-7.60(m, 3H), 7.66(d, J=8.3Hz, 1H), 7.96(d, J=6.4Hz, 2H)

15

Example 44

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(4-oxovalerylamino)valerylamino]-3-phenylcyclopropanone (compd. No. 137 in Table 1)

20

mp: 89-93 °C

IR(KBr, cm⁻¹): 3299, 1856, 1719, 1643

25

NMR(CDCl₃, δ): 0.76(d, J=6.1Hz, 3H), 0.77(d, J=5.8Hz, 3H), 0.95(d, J=6.7Hz, 3H), 1.08(d, J=6.6Hz, 3H), 1.28(m, 1H), 1.48(m, 2H), 2.16(s, 3H), 2.27-2.50(m, 3H), 2.65-2.80(m, 1H), 2.85-3.05(m, 1H), 3.66(m, 1H), 4.35(m, 1H), 5.10(m, 1H), 6.18(d, J=8.5Hz, 1H), 6.55(d, J=7.6Hz, 1H), 7.45-7.60(m, 3H), 7.62(d, J=8.0Hz, 1H), 7.98(dd, J=7.9Hz, 1.7Hz, 2H)

Example 45

30

Preparation of 2-[(1S, 2S)-2-[(S)-2-(3-benzoylpropionylamino)-4-methylvalerylamino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 140 in Table 1)

mp: 83-88 °C

IR(KBr, cm⁻¹): 3292, 1856, 1684, 1641

35

NMR(CDCl₃, δ): 0.78(d, J=6.1Hz, 3H), 0.79(d, J=5.9Hz, 3H), 0.90(d, J=6.7Hz, 3H), 1.05(d, J=6.6Hz, 3H), 1.31(m, 1H), 1.48-1.68(m, 2H), 2.40(m, 1H), 2.54(m, 2H), 3.22-3.48(m, 1H), 3.42-3.75(m, 2H), 4.38(m, 1H), 5.05(m, 1H), 6.09(m, 1H), 6.57(d, J=7.5Hz, 1H), 7.35-7.60(m, 6H), 7.74(d, J=7.8Hz, 1H), 7.90-8.05(m, 4H)

Example 46

40

Preparation of 2-[(1S, 2S)-2-[(S)-2-(3-ethoxycarbonylpropionylamino)-4-methylvalerylamino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 142 in Table 1)

mp: 111-112 °C

45

IR(KBr, cm⁻¹): 3293, 1856, 1738, 1643

NMR(CDCl₃, δ): 0.70-0.90(m, 6H), 0.97(d, J=6.6Hz, 3H), 1.08(d, J=6.6Hz, 3H), 1.15-1.35(m, 1H), 1.25(t, J=7.2Hz, 3H), 1.40-1.60(m, 2H), 2.30-2.65(m, 4H), 2.70-2.90(m, 1H), 3.57(m, 1H), 4.09(m, 2H), 4.39(m, 1H), 5.09(m, 1H), 6.12(s, 1H), 6.47(d, J=7.1Hz, 1H), 7.45-7.60(m, 3H), 7.66(d, J=7.5Hz, 1H), 7.99(dd, J=7.5Hz, 1.0Hz, 2H)

50

Example 47

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-succinylaminovalerylamino]butyl]-3-phenylcyclopropanone (compd. No. 143 in Table 1)

55

mp: 104-106 °C(dec.)

IR(KBr, cm⁻¹): 3297, 1858, 1719, 1650, 1630

NMR(CD₃OD, δ): 0.56(d, J=6.7Hz, 3H), 0.63(d, J=6.7Hz, 3H), 0.97(d, J=6.9Hz, 3H), 1.08(d, J=6.8Hz, 3H),

1.05-1.33(m, 2H), 1.40(m, 1H), 2.09(m, 1H), 2.35-2.60(m, 4H), 4.0(m, 1H), 4.22(m, 1H), 5.20(d, J=2.9Hz, 1H), 7.47-7.65(m, 3H), 7.90-8.10(m, 3H)

Example 48

5

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenoxyacetylaminovaleryl-amino)butyl]-3-phenylcyclopropenone (compd. No. 148 in Table 1)

mp: 138-139 °C

10

IR(KBr, cm⁻¹): 3290, 1856, 1648, 1620

NMR(CDCl₃, δ): 0.78(d, J=5.8Hz, 6H), 1.02(d, J=6.7Hz, 3H), 1.09(d, J=6.6Hz, 3H), 1.30-1.60(m, 3H), 2.38-(m, 1H), 3.64(m, 1H), 4.26(d, J=15Hz, 1H), 4.37(d, J=15Hz, 1H), 4.49(m, 1H), 5.14(m, 1H), 6.12(m, 1H), 6.84(d, J=8.8Hz, 2H), 6.90(d, J=8.8Hz, 1H), 7.01(t, J=7.4Hz, 1H), 7.25-7.38(m, 2H), 7.38-7.53(m, 3H), 7.66(d, J=7.6Hz, 1H), 7.85-7.98(m, 2H)

15

Example 49

Preparation of 2-[(1R, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenoxyacetylaminovaleryl-amino)butyl]-3-phenylcyclopropenone (compd. No. 148 in Table 1)

20

mp: 74-84 °C

IR(KBr, cm⁻¹): 3300, 1859, 1658, 1627

25

NMR(CDCl₃, δ): 0.64(d, J=6.3Hz, 6H), 1.06(d, J=6.6Hz, 3H), 1.15(d, J=6.7Hz, 3H), 1.30-1.65(m, 3H), 2.14-(m, 1H), 4.03(m, 1H), 4.39(d, J=15Hz, 1H), 4.47(d, J=15Hz, 1H), 4.51(m, 1H), 5.15(dd, J=6.6Hz, 2.8Hz, 1H), 5.26(d, J=6.6Hz, 1H), 6.85-6.95(m, 3H), 7.02(t, J=7.4Hz, 1H), 7.20-7.40(m, 3H), 7.45-7.60(m, 3H), 8.01(dd, J=7.8Hz, 1.3Hz, 2H)

Example 50

30

Preparation of 2-[(1S, 2S)-2-((S)-2-(2-chlorophenoxyacetylamin)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 152 in Table 1)

mp: 101 °C

IR(KBr, cm⁻¹): 3287, 1856, 1653, 1624

35

NMR(CDCl₃, δ): 0.80(d, J=5.2Hz, 3H), 0.82(d, J=5.1Hz, 3H), 1.03(d, J=6.6Hz, 3H), 1.10(d, J=6.6Hz, 3H), 1.35-1.60(m, 3H), 2.38(m, 1H), 3.68(m, 1H), 4.30(d, J=15Hz, 1H), 4.40(d, J=15Hz, 1H), 4.45(m, 1H), 5.14-(dd, J=7.8Hz, 4.1Hz, 1H), 6.17(d, J=8.4Hz, 1H), 6.81(d, J=8.2Hz, 1H), 6.97(t, J=7.7Hz, 1H), 7.07(d, J=7.7Hz, 1H), 7.22(t, J=7.6Hz, 1H), 7.32-7.48(m, 4H), 7.71(d, J=7.7Hz, 1H), 7.85-7.95(m, 2H)

40

Example 51

Preparation of 2-[(1S, 2S)-2-((S)-2-(4-chlorophenoxyacetylamin)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 154 in Table 1)

mp: 88-90 °C

45

IR(KBr, cm⁻¹): 3295, 1856, 1653, 1624

NMR(CDCl₃, δ): 0.79(d, J=3.7Hz, 6H), 1.02(d, J=6.6Hz, 3H), 1.10(d, J=6.6Hz, 3H), 1.33-1.60(m, 3H), 2.36-(m, 1H), 3.65(m, 1H), 4.21(d, J=15Hz, 1H), 4.34(d, J=15Hz, 1H), 4.51(m, 1H), 5.14(dd, J=8.3Hz, 4.1Hz, 1H), 6.12(d, J=8.3Hz, 1H), 6.78(d, J=8.9Hz, 2H), 6.88(d, J=8.3Hz, 1H), 7.24(d, J=8.9Hz, 2H), 7.35-7.55(m, 3H), 7.69(d, J=8.0Hz, 1H), 7.90(dd, J=6.6Hz, 2.5Hz, 2H)

50

Example 52

Preparation of 2-[(1S, 2S)-2-((S)-2-(2,3-dichlorophenoxyacetylamin)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 155 in Table 1)

55

mp: 121-123 °C

IR(KBr, cm⁻¹): 3291, 1856, 1651, 1624

NMR(CDCl₃, δ): 0.81(d, J=5.0Hz, 3H), 0.83(d, J=5.1Hz, 3H), 1.03(d, J=6.6Hz, 3H), 1.11(d, J=6.6Hz, 3H),

1.38-1.63(m, 3H), 2.38(m, 1H), 3.67(m, 1H), 4.31(d, J = 14Hz, 1H), 4.40(d, J = 14Hz, 1H), 4.45(m, 1H), 5.15-
(dd, J = 8.3Hz, 4.0Hz, 1H), 6.20(d, J = 8.3Hz, 1H), 6.73(m, 1H), 7.03(d, J = 8.3Hz, 1H), 7.07-7.22(m, 2H), 7.35-
7.55(m, 3H), 7.74(d, J = 8.2Hz, 1H), 7.88(d, J = 5.2Hz, 2H)

5 Example 53

Preparation of 2-[(1S, 2S)-1-hydroxy-2-[(S)-2-(2-methoxyphenoxyacetyl-amino)-4-methylvaleryl-amino]]-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 161 in Table 1)

10 mp: 106-108 °C

IR(KBr, cm⁻¹): 3278, 1854, 1672, 1645

NMR(CDCl₃, δ): 0.70-0.85(m, 6H), 0.96(d, J = 6.7Hz, 3H), 1.05(d, J = 6.6Hz, 3H), 1.30-1.55(m, 3H), 2.36(m, 1H), 3.57(m, 1H), 3.84(s, 3H), 4.41(m, 1H), 4.41(d, J = 15Hz, 1H), 4.49(d, J = 15Hz, 1H), 5.10(dd, J = 7.3Hz, 4.6Hz, 1H), 6.08(d, J = 8.2Hz, 1H), 6.82-6.95(m, 3H), 6.95-7.08(m, 1H), 7.33-7.57(m, 5H), 7.94(dd, J = 6.1Hz, 1.7Hz, 2H)

Example 54

Preparation of 2-[(1S, 2S)-2-[(S)-2-benzyloxyacetyl-amino-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 166 in Table 1)

mp: 59-69 °C

IR(KBr, cm⁻¹): 3293, 1856, 1651, 1623

NMR(CDCl₃, δ): 0.65-0.85(m, 6H), 0.99(d, J = 6.6Hz, 3H), 1.06(d, J = 6.6Hz, 3H), 1.30-1.60(m, 3H), 2.29(m, 1H), 3.75(m, 1H), 3.76(d, J = 15Hz, 1H), 3.88(d, J = 15Hz, 1H), 4.30-4.55(m, 3H), 5.08(m, 1H), 6.12(m, 1H), 6.95(d, J = 8.4Hz, 1H), 7.20-7.40(m, 5H), 7.40-7.60(m, 3H), 7.69(d, J = 8.1Hz, 1H), 7.93(d, J = 6.5Hz, 2H)

Example 55

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(3-phenoxypropionyl-amino)-valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 167 in Table 1)

mp: 92-95 °C

IR(KBr, cm⁻¹): 3291, 1856, 1643, 1605

NMR(CDCl₃, δ): 0.73(d, J = 6.3Hz, 6H), 0.89(d, J = 6.7Hz, 3H), 0.99(d, J = 6.6Hz, 3H), 1.25-1.58(m, 3H), 2.31-
(m, 1H), 2.59(t, J = 4.0Hz, 2H), 3.51(m, 1H), 4.16(m, 2H), 4.41(m, 1H), 5.07(dd, J = 8.1Hz, 4.2Hz, 1H), 6.28(d, J = 8.3Hz, 1H), 6.69(d, J = 8.1Hz, 1H), 6.87(d, J = 8.7Hz, 2H), 6.95(t, J = 7.6Hz, 1H), 7.19-7.35(m, 2H), 7.40-
7.60(m, 4H), 7.96(dd, J = 6.8Hz, 1.4Hz, 2H)

40 Example 56

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-phenylthioacetyl-aminovaleryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 168 in Table 1)

45 mp: 133 °C

IR(KBr, cm⁻¹): 3287, 1854, 1643, 1625

NMR(CDCl₃, δ): 0.55-0.80(m, 6H), 0.93(d, J = 6.6Hz, 3H), 1.06(d, J = 6.6Hz, 3H), 1.05-1.40(m, 3H), 2.28(m, 1H), 3.43(d, J = 17Hz, 1H), 3.58(d, J = 17Hz, 1H), 3.62(m, 1H), 4.33(m, 1H), 5.11(dd, J = 8.3Hz, 4.1Hz, 1H), 6.15(m, 1H), 7.08-7.35(m, 6H), 7.35-7.60(m, 4H), 7.95(dd, J = 7.5Hz, 1.6Hz, 2H)

50 Example 57

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(3-phenylsulfonylpropionyl-amino)-valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 170 in Table 1)

55

mp: 100-106 °C

IR(KBr, cm⁻¹): 3295, 1856, 1644

NMR(CDCl₃, δ): 0.74(d, J = 4.2Hz, 6H), 0.99(d, J = 6.8Hz, 3H), 1.07(d, J = 6.8Hz, 3H), 1.25-1.65(m, 3H), 2.38-

(m, 1H), 2.69(m, 2H), 3.27-3.43(m, 1H), 3.43-3.65(m, 2H), 4.37(m, 1H), 5.14(dd, J=8.9Hz, 5.0Hz, 1H), 6.18-(d, J=8.9Hz, 1H), 7.18(d, J=7.6Hz, 1H), 7.40-7.60(m, 5H), 7.67(t, J=7.4Hz, 2H), 7.90(d, J=7.2Hz, 2H), 7.98(d, J=6.4Hz, 2H)

5 Example 58

Preparation of 2-[(1S, 2S)-2-[(S)-2-benzoylamino-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 171 in Table 1)

10 mp: 150-154 °C

IR(KBr, cm⁻¹): 3297, 1856, 1632

NMR(CDCl₃, δ): 0.63-0.80(m, 6H), 0.91(d, J=6.5Hz, 3H), 0.93(d, J=6.5Hz, 3H), 1.35-1.65(m, 3H), 2.22(m, 1H), 3.42(m, 1H), 4.48(m, 1H), 4.78(m, 1H), 6.23(d, J=7.8Hz, 1H), 7.28-7.55(m, 6H), 7.60-7.68(m, 3H), 7.81-(d, J=8.2Hz, 1H), 7.85-7.95(m, 2H)

15

Example 59

Preparation of 2-[(1S, 2S)-2-[(S)-2-(2,6-difluorobenzoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 175 in Table 1)

20

mp: 111-122 °C

IR(KBr, cm⁻¹): 3300, 1858, 1647, 1626

NMR(CDCl₃, δ): 0.72(d, J=6.3Hz, 3H), 0.74(d, J=6.2Hz, 3H), 1.04(d, J=6.8Hz, 3H), 1.10(d, J=6.7Hz, 3H), 1.30-1.65(m, 3H), 2.33(m, 1H), 3.73(m, 1H), 4.57(m, 1H), 5.01(d, J=4.0Hz, 1H), 6.82(dd, J=8.0Hz, 7.9Hz, 2H), 7.26(m, 1H), 7.37-7.55(m, 4H), 7.64(d, J=8.3Hz, 1H), 7.91(d, J=6.7Hz, 2H)

25

Example 60

Preparation of 2-[(1S, 2S)-2-[(S)-2-(2-chlorobenzoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 178 in Table 1)

30

mp: 99-104 °C

IR(KBr, cm⁻¹): 3297, 1856, 1637

NMR(CDCl₃, δ): 0.76(d, J=5.7Hz, 3H), 0.78(d, J=5.1Hz, 3H), 1.04(d, J=6.6Hz, 3H), 1.09(d, J=6.6Hz, 3H), 1.38-1.65(m, 3H), 2.32(m, 1H), 3.72(m, 1H), 4.59(m, 1H), 5.05(dd, J=8.4Hz, 4.3Hz, 1H), 6.14(d, J=8.4Hz, 1H), 7.05-7.35(m, 4H), 7.35-7.58(m, 4H), 7.71(d, J=8.2Hz, 1H), 7.91(d, J=6.7Hz, 2H)

35

Example 61

Preparation of 2-[(1S, 2S)-2-[(S)-2-(3-chlorobenzoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 179 in Table 1)

40

mp: 179 °C

IR(KBr, cm⁻¹): 3297, 1856, 1634

NMR(CDCl₃, δ): 0.71(d, J=6.2Hz, 3H), 0.74(d, J=6.4Hz, 3H), 0.90(d, J=6.7Hz, 3H), 0.93(d, J=8.8Hz, 3H), 1.30-1.70(m, 3H), 2.19(m, 1H), 3.44(m, 1H), 4.46(m, 1H), 4.83(m, 1H), 6.20(m, 1H), 7.15-7.35(m, 1H), 7.35-7.55(m, 4H), 7.64(d, J=7.7Hz, 1H), 7.75(s, 1H), 7.80-8.03(m, 4H)

45

Example 62

Preparation of 2-[(1S, 2S)-2-[(S)-2-(4-chlorobenzoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 180 in Table 1)

50

mp: 116-120 °C

IR(KBr, cm⁻¹): 3297, 1856, 1631

NMR(CDCl₃, δ): 0.71(d, J=5.5Hz, 3H), 0.73(d, J=5.4Hz, 3H), 0.89(d, J=6.6Hz, 3H), 0.95(d, J=6.6Hz, 3H), 1.30-1.65(m, 3H), 2.21(m, 1H), 3.51(m, 1H), 4.49(m, 1H), 4.87(m, 1H), 6.26(d, J=8.6Hz, 1H), 7.28(d, J=7.5Hz, 2H), 7.38-7.58(m, 3H), 7.67(d, J=7.5Hz, 2H), 7.70-7.95(m, 4H)

55

Example 63

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-toluoylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 184 in Table 1)

mp: 101-105 °C

IR(KBr, cm⁻¹): 3295, 1856, 1656, 1631

NMR(CDCl₃, δ): 0.75(d, J=5.9Hz, 3H), 0.76(d, J=5.8Hz, 3H), 1.02(d, J=6.7Hz, 3H), 1.06(d, J=6.7Hz, 3H), 1.40-1.65(m, 3H), 2.25(m, 1H), 2.30(s, 3H), 3.66(m, 1H), 4.52(m, 1H), 4.88(dd, J=8.9Hz, 4.0Hz, 1H), 6.14(d, J=8.9Hz, 1H), 7.01-7.08(m, 3H), 7.08-7.32(m, 2H), 7.38-7.60(m, 3H), 7.78(d, J=7.1Hz, 1H), 7.87(dd, J=8.2Hz, 1.5Hz, 2H)

Example 64

Preparation of 2-[(1S, 2S)-1-hydroxy-2-{2-(4-methoxybenzoylamino)-4-methylvaleryl-amino}-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 190 in Table 1)

IR(KBr, cm⁻¹): 3297, 1856, 1628

NMR(CDCl₃, δ): 0.62-0.90(m, 6H), 0.90-1.05(m, 6H), 1.30-1.60(m, 3H), 2.21(m, 1H), 3.46(m, 1H), 3.80(s, 3H), 4.49(m, 1H), 4.70-4.95(m, 1H), 6.20-6.50(m, 1H), 6.83(d, J=8.9Hz, 2H), 7.33-7.58(m, 4H), 7.68-7.95(m, 3H), 7.87(d, J=7.8Hz, 2H)

Example 65

Preparation of 2-[(1S, 2S)-1-hydroxy-2-[(S)-2-(4-methoxycarbonylbenzoylamino)-4-methylvaleryl-amino]-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 191 in Table 1)

mp: 125-128 °C

IR(KBr, cm⁻¹): 3301, 1856, 1728, 1634

NMR(CDCl₃, δ): 0.71(d, J=5.5Hz, 3H), 0.73(d, J=5.3Hz, 3H), 0.89(d, J=6.9Hz, 3H), 0.93(d, J=7.0Hz, 3H), 1.33-1.65(m, 3H), 2.18(m, 1H), 3.51(m, 1H), 3.92(s, 3H), 4.52(m, 1H), 4.84(dd, J=8.9Hz, 3.5Hz, 1H), 6.25(d, J=8.9Hz, 1H), 7.35-7.55(m, 3H), 7.76(d, J=8.3Hz, 2H), 7.85-8.03(m, 6H)

Example 66

Preparation of 2-[(1S, 2S)-2-[(S)-2-(1-acetyl-4-piperidyl)carbonylamino]-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 196 in Table 1)

mp: 120-124 °C

IR(KBr, cm⁻¹): 3300, 1860, 1630

NMR(CDCl₃, δ): 0.72(d, J=2.7Hz, 6H), 0.96(d, J=6.6Hz, 3H), 1.08(d, J=6.9Hz, 3H), 1.30-1.90(m, 7H), 2.06-(s, 3H), 1.95-2.40(m, 2H), 2.55(m, 1H), 3.01(m, 1H), 3.70-3.93(m, 2H), 4.35-4.60(m, 2H), 5.14(m, 1H), 6.15(m, 1H), 6.70(t, J=8.8Hz, 1H), 7.43-7.65(m, 4H), 7.97(d, J=6.8Hz, 2H)

Example 67

Preparation of 2-[(1S, 2S)-2-[(S)-2-(2-furoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 197 in Table 1)

mp: 101-105 °C

IR(KBr, cm⁻¹): 3300, 1857, 1640

NMR(CDCl₃, δ): 0.80(d, J=5.8Hz, 6H), 1.01(d, J=7.1Hz, 3H), 1.08(d, J=7.0Hz, 3H), 1.40-1.65(m, 3H), 2.37-(m, 1H), 3.67(m, 1H), 4.58(m, 1H), 5.14(d, J=4.4Hz, 1H), 6.43(dd, J=3.7Hz, 1.8Hz, 1H), 6.79(d, J=8.7Hz, 1H), 7.01(d, J=3.7Hz, 1H), 7.35(d, J=1.8Hz, 1H), 7.40-7.55(m, 3H), 7.78(d, J=8.2Hz, 1H), 7.91(dd, J=8.1Hz, 1.5Hz, 2H)

Example 68

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-thenoylamino)valeryl-amino]butyl]-3-phenylcyclopropanone (compd. No. 200 in Table 1)

mp: 171-172 °C

5 IR(KBr, cm⁻¹): 3301, 1856, 1665, 1624

NMR(CDCl₃, δ): 0.69(d, J=6.9Hz, 3H), 0.72(d, J=6.6Hz, 3H), 0.87(d, J=6.6Hz, 3H), 0.92(d, J=6.6Hz, 3H), 1.30-1.70(m, 3H), 2.15(m, 1H), 3.62(m, 1H), 4.48(m, 1H), 4.94(dd, J=8.4Hz, 3.1Hz, 1H), 6.34(d, J=8.4Hz, 1H), 6.99(dd, J=4.5Hz, 4.3Hz, 1H), 7.38-7.62(m, 4H), 7.66(dd, J=3.5Hz, 1H), 7.68-8.03(m, 4H)

10 Example 69

Preparation of 2-[(1S, 2S)-2-[(S)-2-(1,3-dimethyl-5-pyrazolylcarbonylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 203 in Table 1)

15 mp: 115-118 °C

IR(KBr, cm⁻¹): 3289, 1856, 1636

NMR(CDCl₃, δ): 0.80(d, J=5.9Hz, 3H), 0.82(d, J=6.0Hz, 3H), 1.01(d, J=6.7Hz, 3H), 1.06(d, J=6.7Hz, 3H), 1.42-1.60(m, 3H), 2.20(s, 3H), 2.37(m, 1H), 3.54(m, 1H), 4.00(s, 3H), 4.50(m, 1H), 5.06(m, 1H), 6.03(s, 1H), 6.27(s, 1H), 6.80(d, J=8.3Hz, 1H), 7.43-7.54(m, 3H), 7.58(d, J=7.8Hz, 1H), 7.89(dd, J=7.8Hz, 1.5Hz, 2H)

20

Example 70

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(6-methyl-2-pyridylcarbonylamino)-valeryl-amino]butyl]-3-phenylcyclopropanone (compd. No. 207 in Table 1)

25

mp: 98-100 °C

IR(KBr, cm⁻¹): 3314, 1856, 1655

NMR(CDCl₃, δ): 0.81(d, J=5.7Hz, 3H), 0.82(d, J=5.9Hz, 3H), 1.02(d, J=6.7Hz, 3H), 1.08(d, J=6.7Hz, 3H), 1.56(m, 3H), 2.42(m, 1H), 2.49(s, 3H), 3.67(m, 1H), 4.56(m, 1H), 5.18(m, 1H), 6.33(d, J=7.8Hz, 1H), 7.22(d, J=7.5Hz, 1H), 7.36-7.44(m, 3H), 7.64(dd, J=7.7Hz, 7.7Hz, 1H), 7.77-7.90(m, 4H), 8.22(d, J=4.1Hz, 1H)

30

Example 71

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-nicotinoylaminovaleryl-amino]butyl]-3-phenylcyclopropanone (compd. No. 209 in Table 1)

35

mp: 108-115 °C(dec.)

IR(KBr, cm⁻¹): 3299, 1856, 1642

NMR(CDCl₃, δ): 0.63-0.80(m, 6H), 0.92(d, J=6.7Hz, 3H), 0.96(d, J=6.8Hz, 3H), 1.34-1.72(m, 3H), 2.23(m, 1H), 3.58(m, 1H), 4.59(m, 1H), 5.30(m, 1H), 6.58(m, 1H), 7.25(m, 1H), 7.35-7.55(m, 3H), 7.92(dd, J=6.7Hz, 1.4Hz, 2H), 8.02-8.18(m, 2H), 8.32(m, 1H), 8.59(dd, J=4.8Hz, 1.5Hz, 1H), 9.11(d, J=1.5Hz, 1H)

40

Example 72

Preparation of 2-[(1S, 2S)-1-hydroxy-2-[(S)-2-isonicotinoylamino-4-methylvaleryl-amino]-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 213 in Table 1)

45

mp: 202-203 °C(dec.)

IR(KBr, cm⁻¹): 3299, 1856, 1647, 1625

NMR(CD₃OD, δ): 0.54(d, J=6.4Hz, 3H), 0.69(d, J=6.4Hz, 3H), 1.01(d, J=6.7Hz, 3H), 1.12(d, J=6.6Hz, 3H), 0.95-1.60(m, 3H), 2.12(m, 1H), 4.07(m, 1H), 4.55(m, 1H), 5.24(d, J=2.2Hz, 1H), 7.45-7.70(m, 3H), 8.07(d, J=8.0Hz, 2H), 8.33(d, J=6.8Hz, 2H), 8.44(d, J=9.7Hz, 1H), 9.57(d, J=6.8Hz, 2H)

50

Example 73

Preparation of 2-[(1S, 2S)-2-[(S)-2-(2-chloroisonicotinoylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 216 in Table 1)

55

mp: 136-138 °C(dec.)

IR(KBr, cm^{-1}): 3299, 1856, 1643

NMR(CDCl_3 , δ): 0.76(d, J = 6.4Hz, 3H), 0.79(d, J = 6.6Hz, 3H), 0.95(d, J = 6.7Hz, 3H), 1.02(d, J = 6.6Hz, 3H), 1.40-1.63(m, 3H), 2.26(m, 1H), 3.50(m, 1H), 4.51(m, 1H), 5.00(d, J = 3.5Hz, 1H), 6.03(s, 1H), 7.43-7.53(m, 4H), 7.62(d, J = 0.6Hz, 1H), 7.75(m, 2H), 7.90(dd, J = 7.9Hz, 1.3Hz, 2H), 8.41(d, J = 5.2Hz, 1H)

Example 74

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-quinolylcarbonylamino)-valeryl-amino]butyl-3-phenylcyclopropenone hydrochloride (compd. No. 219 in Table 1)

mp: 156-157 °C(dec.)

IR(KBr, cm^{-1}): 3252, 1854, 1684, 1620

NMR(CD_3OD , δ): 0.60(d, J = 6.4Hz, 3H), 0.74(d, J = 6.4Hz, 3H), 1.02(d, J = 6.7Hz, 3H), 1.12(d, J = 6.6Hz, 3H), 1.08-1.33(m, 1H), 1.52(m, 2H), 2.15(m, 1H), 4.09(dd, J = 9.8Hz, 2.4Hz, 1H), 4.66(m, 1H), 5.25(d, J = 2.3Hz, 1H), 7.40-7.58(m, 3H), 7.92(m, 1H), 8.02-8.17(m, 3H), 8.26(d, J = 8.3Hz, 1H), 8.36(dd, J = 8.6Hz, 1.6Hz, 2H), 9.02(d, J = 8.5Hz, 1H)

Example 75

Preparation of 2-[(1S, 2S)-2-[(S)-2-(3-benzylureido)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 225 in Table 1)

mp: 160 °C

IR(KBr, cm^{-1}): 3308, 1856, 1628

NMR(CD_3OD , δ): 0.53(d, J = 6.6Hz, 3H), 0.62(d, J = 6.5Hz, 3H), 0.95(d, J = 6.7Hz, 3H), 1.08(d, J = 6.7Hz, 3H), 0.95-1.25(m, 2H), 1.39(m, 1H), 2.07(m, 1H), 4.01(dd, J = 9.5Hz, 2.4Hz, 1H), 4.13(dd, J = 9.9Hz, 4.9Hz, 1H), 4.20(d, J = 14Hz, 1H), 4.26(d, J = 14Hz, 1H), 5.19(d, J = 2.4Hz, 1H), 7.13-7.33(m, 5H), 7.50-7.70(m, 3H), 7.07-(dd, J = 7.6Hz, 1.8Hz, 2H)

Example 76

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(3-phenylureido)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 227 in Table 1)

mp: 165-169 °C(dec.)

IR(KBr, cm^{-1}): 3318, 1856, 1645, 1620

NMR(CD_3OD , δ): 0.55(d, J = 6.6Hz, 3H), 0.66(d, J = 6.5Hz, 3H), 0.99(d, J = 6.7Hz, 3H), 1.10(d, J = 6.7Hz, 3H), 1.0-1.35(m, 2H), 1.48(m, 1H), 2.11(m, 1H), 4.03(dd, J = 9.6Hz, 2.4Hz, 1H), 4.20(dd, J = 10Hz, 5.0Hz, 1H), 5.22(d, J = 2.4Hz, 1H), 6.94(t, J = 7.2Hz, 1H), 7.15-7.33(m, 4H), 7.50-7.67(m, 3H), 8.07(dd, J = 8.2Hz, 1.8Hz, 2H)

Example 77

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-propylsulfonylaminovaleryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 232 in Table 1)

mp: 195-196 °C

IR(KBr, cm^{-1}): 3450, 3250, 1858, 1823, 1663, 1630

NMR($\text{DMSO}-d_6$, δ): 0.37(d, J = 6.9Hz, 3H), 0.58(d, J = 7.4Hz, 3H), 0.70-1.15(m, 8H), 1.03(d, J = 7.0Hz, 3H), 1.50-1.80(m, 3H), 1.96(m, 1H), 2.72(m, 2H), 3.82(m, 1H), 3.93(m, 1H), 5.11(m, 1H), 6.34(d, J = 5.4Hz, 1H), 7.14(d, J = 10Hz, 1H), 7.50-7.65(m, 3H), 7.93(d, J = 7.4Hz, 2H), 8.08(d, J = 10Hz, 1H)

Example 78

Preparation of 2-[(1S, 2S)-2-[(S)-2-benzylsulfonylamino-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 237 in Table 1)

mp: 197 °C(dec.)

IR(KBr, cm⁻¹): 3314, 1856, 1678, 1624

NMR(DMSO-d₆): 0.39(d, J = 6.6Hz, 3H), 0.57(d, J = 6.5Hz, 3H), 0.78-1.0(m, 2H), 0.95(d, J = 6.7Hz, 3H), 1.04-
 5 (d, J = 6.6Hz, 3H), 1.42(m, 1H), 1.99(m, 1H), 3.83-4.07(m, 2H), 4.05(d, J = 14Hz, 1H), 4.14(d, J = 14Hz, 1H),
 5.14(m, 1H), 6.38(m, 1H), 7.33(s, 5H), 7.20-7.45(m, 1H), 7.53-7.73(m, 3H), 7.94(dd, J = 7.1Hz, 1.5Hz, 2H),
 8.14(d, J = 9.4Hz, 1H)

Example 79

10 Preparation of 2-[(1R, 2S)-2-((S)-2-benzylsulfonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 237 in Table 1)

mp: 122-124 °C

IR(KBr, cm⁻¹): 3280, 1858, 1662, 1625

15 NMR(CDCl₃, δ): 0.66(d, J = 6.4Hz, 3H), 0.69(d, J = 6.3Hz, 3H), 0.87(m, 1H), 1.10(d, J = 6.6Hz, 3H), 1.14(d, J = 6.7Hz, 3H), 1.47(m, 2H), 2.17(m, 1H), 3.77(m, 1H), 4.08-4.23(m, 3H), 4.92(d, J = 6.4Hz, 1H), 5.14(m, 1H), 5.60(d, J = 8.5Hz, 1H), 7.18(d, J = 8.3Hz, 1H), 7.31(s, 5H), 7.41(t, J = 7.6Hz, 2H), 7.53(t, J = 7.2Hz, 1H), 7.93-
 (d, J = 7.2Hz, 2H)

20 Example 80

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)butyl]-3-phenylcyclopropanone (compd. No. 239 in Table 1)

25 mp: 207 °C(dec.)

IR(KBr, cm⁻¹): 3450, 3300, 1858, 1665, 1625

NMR(CD₃OD, δ): 0.38(d, J = 6.6Hz, 3H), 0.40(d, J = 6.5Hz, 3H), 0.78(d, J = 6.7Hz, 3H), 1.02(d, J = 6.6Hz, 3H), 0.75-0.95(m, 2H), 1.34(m, 1H), 1.97(m, 1H), 3.71(dd, J = 10Hz, 4.4Hz, 1H), 3.92(dd, J = 9.4Hz, 2.5Hz, 1H), 5.14(d, J = 2.5Hz, 1H), 7.42-7.70(m, 6H), 7.81(dd, J = 8.4Hz, 1.6Hz, 2H), 8.03(dd, J = 7.6Hz, 1.2Hz, 2H)

30

Example 81

Preparation of 2-[(1R, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)butyl]-3-phenylcyclopropanone (compd. No. 239 in Table 1)

35

mp: 193-194 °C(dec.)

IR(KBr, cm⁻¹): 3300, 1860, 1664, 1627

NMR(CDCl₃, δ): 0.45(d, J = 5.9Hz, 3H), 0.69(d, J = 6.0Hz, 3H), 0.99(d, J = 6.6Hz, 3H), 1.11(d, J = 6.6Hz, 3H), 1.30-1.55(m, 3H), 2.10(m, 1H), 3.64(m, 1H), 4.06(m, 1H), 4.81(d, J = 8.0Hz, 1H), 5.11(dd, J = 7.9Hz, 3.2Hz, 1H), 6.04(d, J = 7.7Hz, 1H), 7.17(d, J = 8.8Hz, 1H), 7.40-7.65(m, 6H), 7.83(d, J = 7.2Hz, 2H), 7.97(d, J = 7.0Hz, 2H)

40

Example 82

45 Preparation of 2-[(1S, 2S)-1-acetoxy-3-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)butyl]-3-phenylcyclopropanone (compd. No. 241 in Table 1)

mp: 202-204 °C(dec.)

IR(KBr, cm⁻¹): 3274, 1863, 1751, 1678, 1630

50 NMR(CDCl₃, δ): 0.58(d, J = 6.2Hz, 3H), 0.68(d, J = 6.4Hz, 3H), 0.88(d, J = 6.8Hz, 3H), 0.92(d, J = 6.8Hz, 3H), 1.30-1.60(m, 3H), 1.92(m, 1H), 2.26(s, 3H), 3.67(m, 1H), 4.32(m, 1H), 5.48(d, J = 7.5Hz, 1H), 5.99(d, J = 5.0Hz, 1H), 6.42(d, J = 9.9Hz, 1H), 7.45-7.65(m, 6H), 7.75-7.90(m, 4H)

Example 83

55

Preparation of 2-[(1S, 2S)-2-((S)-2-(4-fluorophenylsulfonylamino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 245 in Table 1)

mp: 207-208 °C(dec.)

IR(KBr, cm⁻¹): 3561, 3272, 1858, 1667, 1634

NMR(CD₃OD, δ): 0.39(d, J = 6.7Hz, 3H), 0.46(d, J = 6.5Hz, 3H), 0.74(d, J = 6.7Hz, 3H), 0.86(m, 1H), 1.02(d, J = 6.7Hz, 3H), 1.03(m, 1H), 1.39(m, 1H), 1.96(m, 1H), 3.72(dd, J = 11Hz, 4.2Hz, 1H), 3.90(m, 1H), 5.14(d, J = 2.4Hz, 1H), 7.15-7.28(m, 2H), 7.50-7.65(m, 3H), 7.78-7.90(m, 2H), 7.98-8.18(m, 2H), 8.09(d, J = 9.6Hz, 1H)

Example 84

Preparation of 2-[(1S, 2S)-2-[(S)-2-(2-chlorophenylsulfonylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 246 in Table 1)

mp: 106-109 °C(dec.)

IR(KBr, cm⁻¹): 3327, 1856, 1624

NMR(CDCl₃, δ): 0.23(d, J = 6.4Hz, 3H), 0.53(d, J = 6.5Hz, 3H), 1.10(d, J = 6.3Hz, 3H), 1.12(d, J = 6.3Hz, 3H), 1.27(m, 2H), 1.41(m, 1H), 2.38(m, 1H), 3.50(m, 1H), 3.93(m, 1H), 5.21(d, J = 4.3Hz, 1H), 7.01(d, J = 6.2Hz, 1H), 7.31-7.42(m, 2H), 7.42-7.60(m, 5H), 8.01(dd, J = 6.8Hz, 1.4Hz, 2H), 8.03(d, J = 7.3Hz, 1H)

Example 85

Preparation of 2-[(1S, 2S)-2-[(S)-2-(4-chlorophenylsulfonylamino)-4-methylvaleryl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 248 in Table 1)

mp: 206 °C(dec.)

IR(KBr, cm⁻¹): 3559, 3268, 1856, 1664, 1634

NMR(CD₃OD, δ): 0.39(d, J = 6.7Hz, 3H), 0.48(d, J = 6.5Hz, 3H), 0.71(d, J = 6.7Hz, 3H), 0.82(m, 1H), 1.01(d, J = 6.6Hz, 3H), 1.05(m, 1H), 1.41(m, 1H), 1.93(m, 1H), 3.74(dd, J = 11Hz, 4.1Hz, 1H), 3.89(m, 1H), 5.13(d, J = 2.4Hz, 1H), 7.50-7.68(m, 5H), 7.75-7.83(m, 2H), 7.98-8.14(m, 3H)

Example 86

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(4-trisulfonylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 251 in Table 1)

mp: 203-205 °C(dec.)

IR(KBr, cm⁻¹): 3318, 1856, 1680, 1626

NMR(CDCl₃, δ): 0.19(d, J = 6.4Hz, 3H), 0.49(d, J = 6.4Hz, 3H), 1.07(d, J = 6.6Hz, 3H), 1.12(d, J = 6.6Hz, 3H), 0.90-1.40(m, 3H), 2.25(m, 1H), 2.38(s, 3H), 3.49(m, 1H), 4.01(m, 1H), 5.23(dd, J = 7.8Hz, 3.8Hz, 1H), 5.82(d, J = 8.0Hz, 1H), 7.13-7.35(m, 3H), 7.44-7.60(m, 4H), 7.73(d, J = 8.2Hz, 2H), 8.0(d, J = 6.4Hz, 2H)

Example 87

Preparation of 2-[(1S, 2S)-1-hydroxy-2-[(S)-2-(4-methoxyphenylsulfonylamino)-4-methylvaleryl-amino]-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 257 in Table 1)

mp: 201-202 °C(dec.)

IR(KBr, cm⁻¹): 3335, 1856, 1680, 1626

NMR(CDCl₃, δ): 0.23(d, J = 6.4Hz, 3H), 0.51(d, J = 6.5Hz, 3H), 1.08(d, J = 6.8Hz, 3H), 1.12(d, J = 6.7Hz, 3H), 0.93-1.37(m, 3H), 2.30(m, 1H), 3.48(m, 1H), 3.83(s, 3H), 3.99(m, 1H), 5.22(dd, J = 8.1Hz, 3.8Hz, 1H), 5.81(d, J = 7.6Hz, 1H), 6.91(d, J = 9.0Hz, 2H), 7.03(d, J = 6.3Hz, 1H), 7.42-7.61(m, 4H), 7.78(d, J = 9.0Hz, 2H), 7.95-8.08(m, 2H)

Example 88

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(1-naphthylsulfonylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 259 in Table 1)

mp: 109-115 °C

IR(KBr, cm^{-1}): 3360, 1856, 1640, 1603

NMR(DMSO- d_6 , δ): -0.01(d, J =4.4Hz, 3H), 0.12(d, J =6.3Hz, 3H), 0.61(d, J =6.1Hz, 3H), 0.89(d, J =6.6Hz, 3H), 0.80-1.22(m, 3H), 1.79(m, 1H), 3.58-3.78(m, 2H), 5.02(m, 1H), 6.24(d, J =4.7Hz, 1H), 7.45-7.65(m, 6H), 7.85-7.99(m, 3H), 7.99-8.07(m, 1H), 8.07-8.12(m, 3H), 8.59(d, J =9.1Hz, 1H)

5

Example 89

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(2-naphthylsulfonylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 260 in Table 1)

10

mp: 214 °C(dec.)

IR(KBr, cm^{-1}): 3551, 3474, 3264, 1856, 1669, 1634

NMR(DMSO- d_6 , δ): 0.23-0.45(m, 9H), 0.75(d, J =6.2Hz, 3H), 0.65-0.85(m, 1H), 0.85-1.05(m, 1H), 1.34(m, 1H), 1.67(m, 1H), 3.64(m, 1H), 3.81(m, 1H), 4.99(m, 1H), 6.24(m, 1H), 7.46-8.10(m, 13H), 8.33(m, 1H)

15

Example 90

Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(3-pyridylsulfonylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 262 in Table 1)

20

mp: 110-112 °C

IR(KBr, cm^{-1}): 3285, 1856, 1672, 1624

NMR(CDCl_3 , δ): 0.13(d, J =6.4Hz, 3H), 0.42(d, J =6.4Hz, 3H), 0.87(m, 1H), 1.11(d, J =6.4Hz, 3H), 1.13(d, J =6.5Hz, 3H), 1.24(m, 2H), 2.24(m, 1H), 3.53(m, 1H), 4.15(m, 1H), 5.29(d, J =2.8Hz, 1H), 5.76(s, 1H), 7.38-7.55(m, 4H), 7.68(s, 1H), 8.01(dd, J =7.6Hz, 1.4Hz, 2H), 8.17(ddd, J =8.1Hz, 1.7Hz, 1.7Hz, 1H), 8.48(d, J =7.0Hz, 1H), 8.74(dd, J =4.8Hz, 1.5Hz, 1H), 9.10(d, J =2.0Hz, 1H)

25

Example 91

30 Preparation of 2-[(1S, 2S)-1-hydroxy-3-methyl-2-[(S)-4-methyl-2-(8-quinolylsulfonylamino)valeryl-amino]butyl]-3-phenylcyclopropenone (compd. No. 265 in Table 1)

mp: 132-137 °C(dec.)

IR(KBr, cm^{-1}): 3287, 1856, 1665, 1626

35 NMR(CDCl_3 , δ): -0.03(d, J =6.3Hz, 3H), 0.41(d, J =6.4Hz, 3H), 0.90-1.30(m, 3H), 1.07(d, J =6.6Hz, 3H), 0.83-(d, J =6.7Hz, 3H), 2.42(m, 1H), 3.52(m, 1H), 3.79(m, 1H), 5.09(dd, J =7.8Hz, 5.8Hz, 1H), 5.70(d, J =7.8Hz, 1H), 6.65(d, J =2.9Hz, 1H), 7.35(d, J =8.4Hz, 1H), 7.40-7.70(m, 5H), 8.02(dd, J =7.4Hz, 2.0Hz, 2H), 8.09(dd, J =8.3Hz, 1.3Hz, 1H), 8.27-8.39(m, 2H), 9.05(dd, J =4.3Hz, 1.6Hz, 1H)

40 Example 92

Preparation of 2-[(1S, 2S)-2-[(S)-2-benzyloxycarbonylamino-3-phenylpropionyl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 276 in Table 1)

45 mp: 175-177 °C

IR(KBr, cm^{-1}): 3300, 1850, 1697, 1648, 1620

NMR(CDCl_3 , δ): 0.85(d, J =6.7Hz, 3H), 0.95(d, J =6.6Hz, 3H), 2.28(m, 1H), 2.80(dd, J =14Hz, 7.9Hz, 1H), 2.99(dd, J =14Hz, 5.9Hz, 1H), 3.60(m, 1H), 4.42(m, 1H), 4.85-5.05(m, 3H), 5.42(d, J =6.2Hz, 1H), 5.99(d, J =8.0Hz, 1H), 7.05-7.35(m, 10H), 7.35-7.60(m, 4H), 7.92-8.03(m, 2H)

50

Example 93

Preparation of 2-[(2S)-2-[(S)-2-benzyloxycarbonylamino-3-phenylpropionyl-amino]-1-hydroxy-3-methylbutyl]-3-phenylcyclopropenone (compd. No. 276 in Table 1)

55

IR(KBr, cm^{-1}): 3300, 1855, 1693, 1645, 1620

NMR(CDCl_3 , δ): 0.84(d, J =6.2Hz, 1.8H), 0.95(d, J =6.7Hz, 1.2H), 1.02(d, J =6.4Hz, 1.8H), 1.05(d, J =6.0Hz, 1.2H), 2.03(m, 0.4H), 2.27(m, 0.6H), 2.75-2.88(m, 0.6H), 2.90-3.05(m, 1.4H), 3.58(m, 0.6H), 4.05(m, 0.4H),

4.41(q, J = 6.8Hz, 1H), 4.73(m, 0.4H), 4.85-5.05(m, 3.6H), 5.27-5.45(m, 1H), 5.94(d, J = 7.9Hz, 0.6H), 7.70(d, J = 7.6Hz, 0.4H), 7.05-7.37(m, 10H), 7.44-7.62(m, 3H), 7.95-8.05(m, 2H)

Example 94

5

Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-phenylcyclopropanone (compd. No. 280 in Table 1)

IR(KBr, cm^{-1}): 3310, 1855, 1790, 1755, 1725

10 NMR(CDCl_3 , δ): 0.65-0.75(m, 1.2H), 0.75-1.05(m, 7.8H), 1.10-2.0(m, 20H), 2.07(s, 1H), 3.65-3.90(m, 2H), 4.0-4.20(m, 1.7H), 4.20-4.35(m, 0.3H), 4.95-5.05(m, 1H), 5.10-5.30(m, 0.3H), 5.45-5.60(m, 0.7H), 5.70-5.85(m, 1H), 7.0-7.25(m, 0.7H), 7.45-7.56(m, 3.3H), 7.95-8.05(m, 2H)

Example 95

15

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-phenylcyclopropanone (compd. No. 281 in Table 1)

IR(KBr, cm^{-1}): 3320, 1855, 1700, 1655, 1625

20 NMR(CDCl_3 , δ): 0.60-0.70(m, 1.8H), 0.70-1.0(m, 7.2H), 1.20-1.65(m, 8H), 1.75-1.95(m, 1H), 2.0(s, 1H), 4.0-4.30(m, 2H), 4.90-5.10(m, 2.7H), 5.35(d, J = 7Hz, 0.3H), 5.70-5.85(m, 1H), 7.05-7.10(m, 0.7H), 7.30(s, 5H), 7.45-7.56(m, 3.3H), 7.95-8.10(m, 2H)

Example 96

25

Preparation of 2-[(2S)-1-hydroxy-2-((S)-4-methyl-2-(2-pyridylmethoxycarbonylamino)valeryl-amino)hexyl]-3-phenylcyclopropanone (compd. No. 282 in Table 1)

IR(KBr, cm^{-1}): 3320, 1855, 1715, 1655, 1628

30 NMR(CDCl_3 , δ): 0.65-0.75(m, 1.8H), 0.75-0.95(m, 7.2H), 1.10-1.70(m, 8H), 1.70-2.0(m, 1H), 2.28(s, 1H), 4.05-4.35(m, 2H), 5.03(s, 1H), 5.16(s, 2H), 6.13(d, J = 8Hz, 1H), 7.13-7.25(m, 1H), 7.31(d, J = 7Hz, 1H), 7.35-7.60(m, 4H), 7.66(t, J = 7Hz, 1H), 7.95-8.05(m, 2H), 8.51(d, J = 5Hz, 1H)

Example 97

35

Preparation of 2-[(RS)-2-((S)-2-tert-butoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-2-methylpropyl]-3-phenylcyclopropanone (compd. No. 290 in Table 1)

IR(KBr, cm^{-1}): 3320, 1858, 1690, 1650, 1625

40 NMR(CDCl_3 , δ): 0.60-0.95(m, 6H), 1.10-1.70(m, 18H), 3.92(m, 1H), 4.65-4.92(m, 2H), 6.63(d, J = 13Hz, 1H), 6.70-6.95(m, 1H), 7.20-7.45(m, 3H), 8.01(d, J = 6.5Hz, 2H)

Example 98

45

Preparation of 2-[(RS)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-2-methylpropyl]-3-phenylcyclopropanone (compd. No. 289 in Table 1)

IR(KBr, cm^{-1}): 3300, 1857, 1695, 1648, 1623

50 NMR(CDCl_3 , δ): 0.65-1.05(m, 8H), 1.05-1.90(m, 18H), 3.68-3.95(m, 2H), 4.0(m, 1H), 4.70-4.88(m, 1H), 4.99(m, 1H), 6.50-6.93(m, 2H), 7.40-7.60(m, 3H), 8.01(dd, J = 5.8Hz, 1.8Hz, 2H)

Example 99

55

Preparation of 2-[(RS)-2-((S)-2-amino-4-methylvaleryl-amino)-1-hydroxy-2-methylpropyl]-3-phenylcyclopropanone hydrochloride (compd. No. 294 in Table 1)

IR(KBr, cm^{-1}): 3250, 1857, 1678, 1615

NMR(CD_3OD , δ): 0.90-1.10(m, 6H), 1.29(s, 1.5H), 1.46(s, 1.5H), 1.51(s, 1.5H), 1.57(s, 1.5H), 1.55-1.85(m,

3H), 3.89(m, 1H), 5.42(s, 0.5H), 5.76(s, 0.5H), 7.55-7.75(m, 3H), 8.0-8.10(m, 2H)

Example 100

- 5 Preparation of 2-[(RS)-1-hydroxy-2-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)propyl]-3-phenylcyclopropenone (compd. No. 297 in Table 1)

IR(KBr, cm^{-1}): 3350, 3290, 3180, 1858, 1654, 1623, 1615

- 10 NMR(CDCl_3 , δ): 0.41(d, J = 6.4Hz, 1.5H), 0.52(d, J = 6.5Hz, 1.5H), 0.56(d, J = 6.6Hz, 1.5H), 0.66(d, J = 6.5Hz, 1.5H), 1.08-1.38(m, 3H), 1.34(s, 1.5H), 1.39(s, 1.5H), 1.49(s, 1.5H), 1.51(s, 1.5H), 3.65(m, 1H), 4.67(d, J = 10Hz, 0.5H), 4.90(d, J = 8.4Hz, 0.5H), 5.73(d, J = 8.2Hz, 0.5H), 6.27(d, J = 8.4Hz, 0.5H), 6.53(d, J = 7.6Hz, 0.5H), 6.90(s, 0.5H), 6.98(d, J = 10Hz, 0.5H), 7.26(s, 0.5H), 7.45-7.65(m, 6H), 7.84(t, J = 6.7Hz, 2H), 8.00(d, J = 7.1Hz, 2H)

15 Example 101

Preparation of 2-[(RS)-1-hydroxy-2-methyl-2-((S)-4-methyl-2-(N-(methylthiomethyl)phenylsulfonylamino)valeryl-amino)propyl]-3-phenylcyclopropenone (compd. No. 298 in Table 1)

- 20 IR(KBr, cm^{-1}): 3350, 3280, 1856, 1670, 1624

- NMR(CDCl_3 , δ): 0.33(d, J = 6.3Hz, 1.5H), 0.38(d, J = 6.3Hz, 1.5H), 0.48(d, J = 6.4Hz, 1.5H), 0.54(d, J = 6.5Hz, 1.5H), 0.65-1.15(m, 3H), 1.51(s, 1.5H), 1.59(s, 1.5H), 1.62(s, 1.5H), 1.71(s, 1.5H), 2.27(s, 1.5H), 2.28(s, 1.5H), 3.92(m, 0.5H), 3.95(m, 0.5H), 4.23(d, J = 15Hz, 0.5H), 4.33(d, J = 15Hz, 0.5H), 4.61(d, J = 15Hz, 0.5H), 4.70(d, J = 15Hz, 0.5H), 4.82(d, J = 9.4Hz, 0.5H), 5.05(d, J = 7.8Hz, 0.5H), 6.28(d, J = 7.9Hz, 0.5H), 6.70(d, J = 9.5Hz, 0.5H), 6.73(s, 0.5H), 7.18(s, 0.5H), 7.45-7.70(m, 6H), 7.80-7.92(m, 2H), 7.99-8.12(m, 2H)

Example 102

- 30 Preparation of 2-[2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-2-methylpropionyl]-3-phenylcyclopropenone (compd. No. 299 in Table 1)

mp: 42-49 °C

IR(KBr, cm^{-1}): 3350, 1768, 1720, 1680

- 35 NMR(CDCl_3 , δ): 0.85-1.35(m, 14H), 1.50(s, 3H), 1.50-1.87(m, 9H), 3.91(m, 2H), 4.52(m, 1H), 4.58-4.63(m, 1H), 5.09(m, 1H), 7.30-7.55(m, 3H), 7.93-8.06(m, 2H)

Example 103

- 40 Preparation of 2-[2-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)propionyl]-3-phenylcyclopropenone (compd. No. 301 in Table 1)

mp: 53-59 °C

IR(KBr, cm^{-1}): 3430, 3260, 1765, 1678

- 45 NMR(CDCl_3 , δ): 0.60(s, 2H), 0.79(s, 1H), 0.95(d, J = 6.4Hz, 3H), 0.97(d, J = 5.1Hz, 3H), 1.23(s, 1H), 1.35(s, 2H), 1.60(m, 2H), 1.85(m, 1H), 3.86(s, 0.3H), 4.11(m, 1H), 4.15(s, 0.7H), 5.24(m, 1H), 7.33-7.62(m, 7H), 7.80-7.95(m, 4H)

Example 104

- 50 Preparation of 2-[(1S, 2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)cyclopropenone (compd. No. 311 in Table 1)

mp: 86-90 °C

IR(KBr, cm^{-1}): 3320, 1858, 1693, 1656, 1625, 1602

- 55 NMR(CDCl_3 , δ): 0.79(d, J = 5.9Hz, 6H), 1.01(d, J = 6.6Hz, 3H), 1.09(d, J = 6.6Hz, 3H), 0.70-1.45(m, 7H), 1.45-1.83(m, 7H), 2.39(m, 1H), 3.50-3.85(m, 3H), 4.08(m, 1H), 5.10(dd, J = 8.6Hz, 4.7Hz, 1H), 5.25(m, 1H), 6.23(m, 1H), 7.19(dd, J = 8.5Hz, 8.5Hz, 2H), 7.47(m, 1H), 8.01(dd, J = 8.5Hz, 5.5Hz, 2H)

Example 105

Preparation of 2-[(1S, 2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)cyclopropenone (compd. No. 311 in Table 1)

mp: 166-168 °C

IR(KBr, cm^{-1}): 3340, 3260, 1861, 1714, 1655, 1625

NMR(CDCl_3 , δ): 0.63-1.03(m, 8H), 1.07(d, J=6.6Hz, 3H), 1.14(d, J=6.6Hz, 3H), 1.03-1.80(m, 12H), 2.14(m, 1H), 3.55-3.85(m, 2H), 3.95-4.15(m, 2H), 5.0-5.23(m, 2H), 5.29(d, J=5.7Hz, 1H), 6.90(d, J=7.0Hz, 1H), 7.18-8.04(dd, J=8.5Hz, 8.5Hz, 2H), 8.04(dd, J=8.5Hz, 5.8Hz, 2H)

Example 106

Preparation of 2-[(1S, 2S)-2-((S)-2-tert-butoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)cyclopropenone (compd. No. 312 in Table 1)

mp: 90-96 °C

IR(KBr, cm^{-1}): 3340, 1858, 1687, 1655, 1635, 1600

NMR(CDCl_3 , δ): 0.77(d, J=6.3Hz, 6H), 1.02(d, J=6.6Hz, 3H), 1.09(d, J=6.4Hz, 3H), 1.20-1.65(m, 3H), 1.39(s, 9H), 2.40(m, 1H), 3.68(m, 1H), 4.07(m, 1H), 5.03-5.31(m, 2H), 6.23(m, 1H), 7.10-7.25(m, 3H), 7.95-8.13(m, 2H)

Example 107

Preparation of 2-[(1R, 2S)-2-((S)-2-tert-butoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)cyclopropenone (compd. No. 312 in Table 1)

IR(KBr, cm^{-1}): 3320, 1859, 1686, 1627

NMR(CDCl_3 , δ): 0.71(d, J=5.7Hz, 6H), 1.08(d, J=6.6Hz, 3H), 1.14(d, J=6.7Hz, 3H), 1.20-1.70(m, 3H), 1.37(s, 9H), 2.14(m, 1H), 3.98-4.15(m, 2H), 4.98(m, 1H), 5.13(m, 1H), 5.39(d, J=5.8Hz, 1H), 6.88(d, J=6.9Hz, 1H), 7.17(dd, J=8.6Hz, 8.6Hz, 2H), 8.03(dd, J=8.6Hz, 5.5Hz, 2H)

Example 108

Preparation of 2-[(1S, 2S)-2-((S)-2-amino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)-cyclopropenone hydrochloride (compd. No. 314 in Table 1)

mp: 141-145 °C(dec.)

IR(KBr, cm^{-1}): 3250, 1857, 1683, 1620, 1600

NMR(CD_3OD , δ): 0.52(d, J=6.5Hz, 3H), 0.74(d, J=6.5Hz, 3H), 1.02(d, J=6.8Hz, 3H), 1.13(d, J=6.6Hz, 3H), 1.0-1.35(m, 2H), 1.43(m, 1H), 2.11(m, 1H), 3.81(m, 1H), 4.11(m, 1H), 5.23(d, J=2.1Hz, 1H), 7.18-7.42(m, 2H), 8.10-8.25(m, 2H)

Example 109

Preparation of 2-[(1R, 2S)-2-((S)-2-amino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(4-fluorophenyl)-cyclopropenone hydrochloride (compd. No. 314 in Table 1)

IR(KBr, cm^{-1}): 3300, 3250, 1860, 1683, 1620, 1603

NMR(CD_3OD , δ): 0.84(d, J=5.9Hz, 3H), 0.88(d, J=5.9Hz, 3H), 1.04(d, J=6.8Hz, 3H), 1.10(d, J=6.8Hz, 3H), 1.58-1.78(m, 3H), 2.16(m, 1H), 3.84(m, 1H), 4.02(m, 1H), 5.17(d, J=6.7Hz, 1H), 7.22-7.35(m, 2H), 8.05-8.16(m, 2H)

Example 110

Preparation of 2-(4-fluorophenyl)-3-[(1R, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-(phenoxyacetyl-amino)valeryl-amino)butyl]cyclopropenone (compd. No. 315 in Table 1)

mp: 75-79 °C

IR(KBr, cm^{-1}): 3410, 3290, 1853, 1650, 1620

NMR(CDCl_3 , δ): 0.66(d, J = 6.2Hz, 6H), 1.05(d, J = 6.6Hz, 3H), 1.14(d, J = 6.7Hz, 3H), 1.36(m, 2H), 1.56(m, 1H), 2.14(m, 1H), 4.02(m, 1H), 4.41(d, J = 15Hz, 1H), 4.48(d, J = 15Hz, 1H), 4.51(m, 1H), 5.13(dd, J = 6.4Hz, 2.5Hz, 1H), 5.29(d, J = 6.4Hz, 1H), 6.91(d, J = 7.9Hz, 2H), 7.03(t, J = 7.4Hz, 1H), 7.12-7.28(m, 3H), 7.31(dd, J = 8.5Hz, 7.5Hz, 2H), 8.04(dd, J = 8.7Hz, 5.5Hz, 2H)

Example 111

10 Preparation of 2-(4-fluorophenyl)-3-[(1S, 2S)-1-hydroxy-3-methyl-2-((S)-4-methyl-2-phenylsulfonylaminovaleryl-amino)butyl]cyclopropenone (compd. No. 317 in Table 1)

mp: 211-212 °C(dec.)

IR(KBr, cm^{-1}): 3400, 3300, 1853, 1670, 1619

15 NMR(CDCl_3 , δ): 0.16(d, J = 6.4Hz, 3H), 0.48(d, J = 6.4Hz, 3H), 0.93(m, 1H), 1.10(d, J = 6.7Hz, 3H), 1.13(d, J = 6.7Hz, 3H), 1.15-1.35(m, 2H), 2.29(m, 1H), 3.47(m, 1H), 4.10(m, 1H), 5.26(dd, J = 7.9Hz, 5.3Hz, 1H), 5.76(d, J = 7.3Hz, 1H), 7.17(dd, J = 8.6Hz, 8.6Hz, 2H), 7.38-7.57(m, 4H), 7.54(d, J = 7.4Hz, 1H), 7.86(d, J = 6.7Hz, 2H), 8.04(dd, J = 8.6Hz, 5.5Hz, 2H)

20 Example 112

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-(4-fluorophenyl)cyclopropenone (compd. No. 319 in Table 1)

25 IR(KBr, cm^{-1}): 3310, 1857, 1698, 1652, 1625, 1600

NMR(CDCl_3 , δ): 0.75-0.98(m, 9H), 1.15-1.95(m, 9H), 3.95-4.30(m, 2H), 4.88-5.12(m, 3H), 5.39(d, J = 7.8Hz, 0.3H), 5.70-5.90(m, 1.7H), 7.08-7.35(m, 3H), 7.30(s, 5H), 7.90-8.10(m, 2H)

Example 113

30 Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxyhexyl]-3-(2-tolyl)cyclopropenone(compd. No. 328 in Table 1)

IR(KBr, cm^{-1}) : 3320, 1845, 1692, 1655, 1615

35 NMR(CDCl_3 , δ): 0.60-1.05(m, 11H), 1.05-2.0(m, 18H), 2.66(s, 2.1H), 2.68(s, 0.9H), 3.65-3.95(m, 2H), 3.95-4.35(m, 2H), 4.95-5.12(m, 1H), 5.24(m, 0.3H), 5.55(m, 0.7H), 7.05-7.35(m, 6H), 7.35-7.50(m, 3H), 8.05-8.20(m, 2H)

Example 114

40 Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-1-hexyl]-3-(5-trimethylsilyl-2-furyl)cyclopropenone (compd. No. 376 in Table 1)

IR(KBr, cm^{-1}): 3310, 1865, 1695, 1655, 1623

45 NMR(CDCl_3 , δ): 0.35(s, 9H), 0.70-1.05(m, 11H), 1.05-2.0(m, 18H), 3.70-3.95(m, 2H), 3.95-4.35(m, 2H), 4.92(m, 1H), 5.0-5.50(m, 1H), 6.45-6.85(m, 1H) δ 6.76(d, J = 3.4Hz, 1H), 7.20-7.28(m, 1H)

Example 115

50 Preparation of 2-[(2S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-1-hexyl]-3-(5-trimethylsilyl-2-thienyl)cyclopropenone (compd. No. 387 in Table 1)

IR(KBr, cm^{-1}): 3320, 1853, 1695, 1655, 1615

55 NMR(CDCl_3 , δ): 0.35(s, 9H), 0.70-1.05(m, 11H), 1.10-2.0(m, 18H), 3.73-3.90(m, 2H), 3.90-4.15(m, 2H), 4.92(d, J = 4.8Hz, 1H), 4.95-5.10(m, 0.3H), 5.10-5.30(m, 0.7H), 6.50-6.65(m, 0.3H), 6.80-6.95(m, 0.7H), 7.29(d, J = 3.6Hz, 1H), 7.82(d, J = 3.6Hz, 0.7H), 7.84(d, J = 3.6Hz, 0.3H)

Example 116

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-3-methylbutyl]-3-(1-hydroxy-1-methylethyl)cyclopropanone (compd. No. 422 in Table 1)

IR(KBr, cm^{-1}): 3316, 1840, 1696, 1655

- 5 NMR(CD_3OD , δ): 0.80-1.0(m, 9.9H), 1.03(d, J=6.6Hz, 2.1H), 1.49(s, 2.1H), 1.52(s, 1.8H), 1.53(s, 2.1H), 1.40-1.80(m, 3H), 1.86-2.20(m, 1H), 4.02(m, 1H), 4.18(m, 1H), 5.03(d, J=2.2Hz, 1H), 5.08(s, 2H), 7.18-7.41(m, 5H), 7.82(d, J=8.3Hz, 0.3H), 7.98(d, J=8.7Hz, 0.7H)

Example 117

10

Preparation of 2-[(2S)-2-((S)-2-benzyloxycarbonylamino-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-(1-hydroxy-1-phenylmethyl)cyclopropanone (compd. No. 444 in Table 1)

IR(KBr, cm^{-1}): 3399, 1846, 1696, 1647

- 15 NMR(CD_3OD , δ): 0.85-1.10(m, 12H), 1.30-1.75(m, 3H), 1.85-2.10(m, 1H), 3.85-4.23(m, 2H), 4.94(m, 0.3H), 5.03(m, 0.7H), 5.08(s, 2H), 5.75-5.90(m, 1H), 7.13-7.55(m, 10H)

Example 118

20

Preparation of 2-[(1S, 2S)-2-((S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 467 in Table 2)

mp: 190-192 °C

IR(KBr, cm^{-1}): 3310, 1848, 1687, 1638, 1625

- 25 NMR(CDCl_3 , δ): 0.77(d, J=4.9Hz, 6H), 0.91(d, J=5.4Hz, 3H), 0.94(d, J=6.1Hz, 3H), 1.01(d, J=6.5Hz, 3H), 1.08(d, J=6.5Hz, 3H), 0.80-1.85(m, 17H), 2.37(m, 1H), 3.62(m, 1H), 3.75-4.0(m, 3H), 4.08(m, 1H), 4.42(m, 1H), 5.10(s, 1H), 5.28(m, 1H), 6.12(m, 1H), 6.88(d, J=7.5Hz, 1H), 7.45-7.85(m, 4H), 7.98(d, J=7.1Hz, 2H)

Example 119

30

Preparation of 2-[(1R, 2S)-2-((S)-2-((S)-2-cyclohexylmethoxycarbonylamino-4-methylvaleryl-amino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 467 in Table 2)

mp: 109-116 °C

- 35 IR(KBr, cm^{-1}): 3300, 1858, 1699, 1645

NMR(CDCl_3 , δ): 0.52(d, J=5.6Hz, 3H), 0.59(d, J=5.6Hz, 3H), 0.85(d, J=6.4Hz, 3H), 0.89(d, J=6.4Hz, 3H), 0.80-1.0(m, 2H), 1.01(d, J=6.4Hz, 3H), 1.13(d, J=6.5Hz, 3H), 1.05-1.40(m, 4H), 1.40-1.85(m, 11H), 2.20(m, 1H), 3.70-3.93(m, 2H), 3.98-4.10(m, 2H), 4.52(m, 1H), 5.15(m, 1H), 5.39(s, 1H), 5.85(d, J=6.5Hz, 1H), 7.01(d, J=6.8Hz, 1H), 7.35-7.65(m, 4H), 8.01(d, J=6.9Hz, 2H)

40

Example 120

Preparation of 2-[(1S, 2S)-2-((S)-2-((S)-2-benzyloxycarbonylamino-3-phenylpropionyl-amino)-4-methylvaleryl-amino)-1-hydroxy-3-methylbutyl]-3-phenylcyclopropanone (compd. No. 478 in Table 2)

45

mp: 128-130 °C

IR(KBr, cm^{-1}): 3297, 1856, 1703, 1649, 1615

- 50 NMR(CDCl_3 , δ): 0.69(d, J=6.0Hz, 3H), 0.74(d, J=5.8Hz, 3H), 1.02(d, J=6.5Hz, 3H), 1.09(d, J=6.5Hz, 3H), 1.25-1.50(m, 3H), 2.42(m, 1H), 2.95-3.10(m, 2H), 3.49(m, 1H), 4.33-4.53(m, 2H), 4.95-5.15(m, 3H), 5.35(m, 1H), 6.25(d, J=8.9Hz, 1H), 6.84(m, 1H), 7.08-7.19(m, 2H), 7.19-7.38(m, 8H), 7.40-7.60(m, 3H), 7.64(d, J=7.1Hz, 1H), 7.96(dd, J=7.7Hz, 1.7Hz, 2H)

The following experiments were conducted to evaluate the biological activity of compound (I) prepared in the above Examples.

55

Experiment 1

Assay of Thiol Protease Inhibitory Activity

Inhibitory activity against papain (P-3125, Sigma) and cathepsin B (C-6286, Sigma) was assayed according to the method described in a literature [Biochemical Journal, 201, 189 (1982)]. Cathepsin L was purified from rat kidney according to the method in a literature [Journal of Biochemistry, 100, 35 (1986)], and the inhibitory activity against it was assayed in the same manner as described in the above literature for cathepsin B. Further, m-calpain was purified from rat brain according to a known method [Journal of Biological Chemistry, 254, p.3210 (1984)] and the inhibitory activity against it was assayed by a method described in a literature [Journal of Biological Chemistry, 259, 12489 (1984)]. The results are shown in Tables 3 and 4. It is evident from Tables 3 and 4 that the compounds in the present invention have a potent inhibitory activity against thiol proteases such as papain, cathepsin B, cathepsin L, m-calpain or the like.

Table 3

Compd. of Ex. No. (Compd.No. in Table 1)	IC ₅₀ (μM)			
	papain	cathepsin B	cathepsin L	m-calpain
1 (No.77)	0.054	0.71	0.00086	1.6
2 (No.77)	22	0.044	0.0012	3.3
4 (No.4)	5.8	0.41	-	0.50
5 (No.10)	> 100	3.0	0.75	2.3
6 (No.15)	0.076	0.16	0.54	0.81
7 (No.16)	0.14	0.32	0.24	2.4
25 (No.83)	13	32	5.7	2.1
26 (No.83)	4.2	43	5.8	1.6
94 (No.280)	0.074	1.0	0.062	2.7
95 (No.281)	13	11	1.27	3.0
96 (No.282)	7.0	28	4.60	5.7
114 (No.376)	0.68	2.5	0.58	5.6
115 (No.387)	0.48	1.5	0.27	11

Table 4 (Inhibitory activity against m-calpain)

Compd. of Ex. No. (Compd. No. in Table 1, 2)	IC ₅₀ (μ M)
9 (No. 2 6)	5.0
2 0 (No. 7 2)	1.3
2 1 (No. 7 2)	3.0
2 9 (No. 9 7)	1.7
3 1 (No. 9 9)	1.3
3 2 (No. 9 9)	1.2
3 3 (No. 1 0 2)	0.84
3 7 (No. 1 1 4)	2.1
3 8 (No. 1 2 0)	4.0
3 9 (No. 1 2 4)	1.9
4 0 (No. 1 2 9)	2.6
4 1 (No. 1 3 2)	1.4
4 2 (No. 1 3 3)	1.5
4 3 (No. 1 3 4)	1.7
4 4 (No. 1 3 7)	3.0
4 5 (No. 1 4 0)	1.0
4 8 (No. 1 4 8)	0.63
5 0 (No. 1 5 2)	1.2
5 1 (No. 1 5 4)	0.75
5 2 (No. 1 5 5)	0.74
5 3 (No. 1 6 1)	2.3
5 4 (No. 1 6 6)	1.1

Table 4 (Inhibitory activity against m-calpain) (continued)

Compd. of Ex. No. (Compd. No. in Table 1, 2)	IC ₅₀ (μ M)
5 5 (No. 1 6 7)	0.80
5 6 (No. 1 6 8)	2.2
5 7 (No. 1 7 0)	3.1
5 9 (No. 1 7 5)	1.6
6 0 (No. 1 7 8)	1.1
6 2 (No. 1 8 0)	1.4
6 3 (No. 1 8 4)	1.6
6 5 (No. 1 9 1)	1.8
6 7 (No. 1 9 7)	0.88
6 8 (No. 2 0 0)	3.1
6 9 (No. 2 0 3)	3.0
7 1 (No. 2 0 9)	1.3
7 2 (No. 2 1 3)	0.40
7 3 (No. 2 1 6)	1.4
7 4 (No. 2 1 9)	0.80
7 5 (No. 2 2 5)	3.3
7 6 (No. 2 2 7)	4.6
7 7 (No. 2 3 2)	0.95
7 8 (No. 2 3 7)	0.44
7 9 (No. 2 3 7)	1.8
8 0 (No. 2 3 9)	0.35
8 1 (No. 2 3 9)	4.3

Table 4 (Inhibitory activity against m-calpain) (continued)

Compd. of Ex. No. (Compd. No. in Table 1, 2)	IC ₅₀ (μ M)
8 3 (No. 2 4 5)	3.0
8 4 (No. 2 4 6)	0.85
8 5 (No. 2 4 8)	0.84
8 6 (No. 2 5 1)	0.75
8 7 (No. 2 5 7)	1.0
8 8 (No. 2 5 9)	0.65
8 9 (No. 2 6 0)	0.46
9 1 (No. 2 6 5)	1.9
105 (No. 3 1 1)	1.5
111 (No. 3 1 7)	2.9
112 (No. 3 1 9)	4.3
118 (No. 4 6 7)	0.84
120 (No. 4 7 8)	1.2

Experiment 2Acute toxicity

A suspension of the compound in the present invention in 0.5% CMC-Na aqueous solution was orally administered to SD female and male rats, and the rats were observed for 7 days. The LD₅₀ value of the compound (I) prepared in Example 1 is: > 2,000 mg/kg.

The following formulation examples are illustrative only.

Formulation 1(1) Tablet

The following ingredients were admixed in a conventional manner and compressed on customary tablet machine.

Compound in Example 1	30 mg
Crystalline cellulose	60 mg
Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft gelatin capsule

The following ingredients were admixed in a conventional manner and filled in soft capsules.

Compound in Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

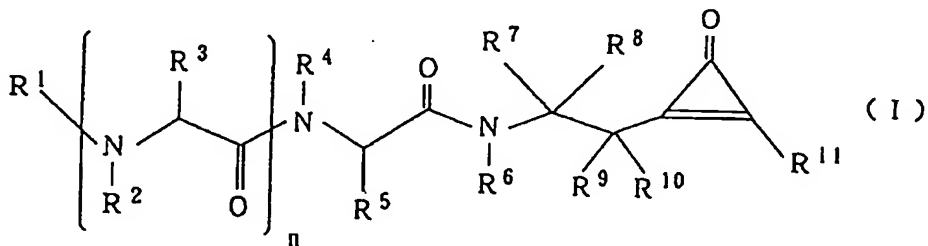
(3) Injection

The following ingredients were admixed in a conventional manner and filled in an ampoule in a volume of 1 ml.

Compound in Example 29	2.5 mg
Sodium chloride	3.5 mg
Distilled water for injection	1 ml

Claims

1. A cyclopropenone derivative of general formula (I):



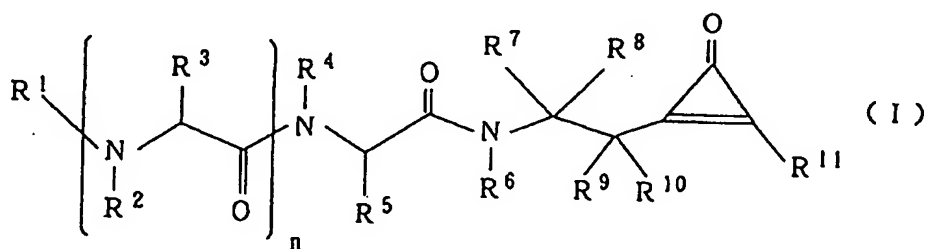
wherein R¹ is hydrogen atom, R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²SO₂- (in which R¹² is C₁-C₂₀ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₅ cycloalkyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₃-C₁₅ cycloalkyloxy group, optionally substituted C₆-C₁₄ aryloxy group, optionally substituted C₆-C₁₄ arylthio group, optionally substituted C₆-C₁₄ arylsulfonyl group, optionally substituted C₇-C₂₀ aralkyloxy group, optionally substituted heterocyclic group, oxo group, hydroxyl group, C₁-C₁₀ alkoxy carbonyl group and carboxyl group; C₃-C₁₅ cycloalkyl group; optionally substituted C₆-C₁₄ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁶ each is independently hydrogen atom or C₁-C₁₀ alkyl group optionally substituted by C₁-C₅ alkoxy group or by C₁-C₅ alkylthio group; R³, R⁵ and R⁷ each is independently hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group or optionally substituted C₇-C₂₀ aralkyl group; R⁸ is hydrogen atom or C₁-C₂₀ alkyl group; R⁷ and R⁸ taken together may form C₃-C₁₅ cycloalkyl group; R⁹ is hydroxy group or C₂-C₁₀ acyloxy group; R¹⁰ is hydrogen atom; or R⁹ and R¹⁰ taken together may form oxo group; R¹¹ is hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₅ cycloalkyl group, C₃-C₁₅ cycloalkyl group, C₂-C₂₀ alkenyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₇-C₂₀ aralkyl group, optionally substituted heterocyclic group or -C(R¹³)(R¹⁴)-OH (in which R¹³ and R¹⁴ each is independently hydrogen atom, C₁-C₂₀ alkyl group, optionally substituted C₇-C₂₀ aralkyl group or optionally substituted C₆-C₁₄ aryl group, or R¹³ and R¹⁴ taken together may form C₃-C₁₅ cycloalkyl group); and n is 0 or 1 or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R¹ is hydrogen atom, R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²-SO₂- (in which R¹² is C₁-C₂₀ alkyl group optionally substituted by one or more substituents selected from the

- group consisting of C₃-C₁₅ cycloalkyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₆-C₁₄ aryloxy group, optionally substituted C₆-C₁₄ arylthio group, optionally substituted C₇-C₂₀ aralkyloxy group, optionally substituted heterocyclic group, oxo group, hydroxy group, C₁-C₁₀ alkoxy carbonyl group and carboxyl group; C₃-C₁₅ cycloalkyl group; optionally substituted C₆-C₁₄ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁵ each is independently hydrogen atom or C₁-C₁₀ alkyl group optionally substituted by C₁-C₅ alkylthio group; R³, R⁵ and R⁷ each is independently hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group or optionally substituted C₇-C₂₀ aralkyl group; R⁸ is hydrogen atom or C₁-C₂₀ alkyl group; and R¹¹ is hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₅ cycloalkyl group, C₃-C₁₅ cycloalkyl group, C₂-C₂₀ alkenyl group, optionally substituted C₆-C₁₄ aryl group, C₇-C₂₀ aralkyl group, optionally substituted heterocyclic group or -C(R¹³)(R¹⁴)-OH (in which R¹³ and R¹⁴ each is independently hydrogen atom, C₁-C₂₀ alkyl group or C₆-C₁₄ aryl group).
3. The compound of claim 2, wherein R¹ is R¹²-CO-, R¹²-O-CO-, R¹²-NH-CO- or R¹²-SO₂- (in which R¹² is C₁-C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₀ cycloalkyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₆-C₁₄ aryloxy group, optionally substituted C₆-C₁₄ arylthio group, optionally substituted C₇-C₂₀ aralkyloxy group, optionally substituted heterocyclic group and oxo group; C₃-C₁₀ cycloalkyl group; C₆-C₁₄ aryl group or optionally substituted heterocyclic group); R², R⁴ and R⁵ each is independently hydrogen atom or C₁-C₁₀ alkyl group; R³, R⁵ and R⁷ each is independently hydrogen atom, C₁-C₁₅ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group or optionally substituted C₇-C₂₀ aralkyl group; R⁸ is hydrogen atom; R⁹ is hydroxy group or C₂-C₁₀ acyloxy group; R¹⁰ is hydrogen atom; and R¹¹ is hydrogen atom, C₁-C₁₅ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group, C₇-C₂₀ aralkyl group, optionally substituted C₆-C₁₀ aryl group or optionally substituted heterocyclic group.
 4. The compound of claim 3, wherein R¹ is R¹²-CO-, R¹²-O-CO- or R¹²-NH-CO- (in which R¹² is C₁-C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₀ cycloalkyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₆-C₁₄ aryloxy group, optionally substituted C₆-C₁₄ arylthio group, optionally substituted C₇-C₂₀ aralkyloxy group, optionally substituted heterocyclic group and oxo group, or optionally substituted C₆-C₁₀ aryl group); and R³, R⁵ and R⁷ each is independently hydrogen atom, C₁-C₁₅ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group or C₇-C₂₀ aralkyl group.
 5. The compound of claim 4, wherein R¹ is R¹²-O-CO- (in which R¹² is C₁-C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₀ cycloalkyl group, C₆-C₁₄ aryl group and heterocyclic group, or C₃-C₁₀ cycloalkyl group); R⁴ and R⁵ each is hydrogen atom, R¹¹ is hydrogen atom, C₁-C₁₅ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group, C₇-C₂₀ aralkyl group or C₆-C₁₀ aryl group; and n is 0.
 6. The compound of claim 4, wherein R¹ is R²-O-CO- (in which R¹² is C₁-C₁₅ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₀ cycloalkyl group, C₆-C₁₄ aryl group and heterocyclic group); R⁴ and R⁵ each hydrogen atom, R⁵ and R⁷ each is independently hydrogen atom, C₁-C₁₅ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group or C₇-C₂₀ aralkyl group; R⁹ is hydroxyl group; R¹¹ is optionally substituted heterocyclic group; and n is 0.
 7. The compound of claim 3, wherein R¹ is R¹²-SO₂-; and R¹¹ is hydrogen atom, optionally substituted C₆-C₁₀ aryl group or optionally substituted heterocyclic group.
 8. The compound of claim 7, wherein R¹² is optionally substituted C₆-C₁₀ aryl group or optionally substituted heterocyclic group.
 9. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
 10. A pharmaceutical composition for treating a disease caused by hypersthenia of thiol protease, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.

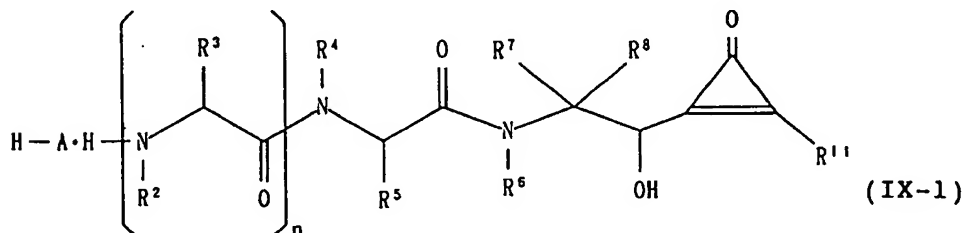
11. A pharmaceutical composition for treating a disease due to the collapse of skeletal muscle, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 5 12. The pharmaceutical composition of claim 11, wherein the disease due to the collapse of skeletal muscle is muscular dystrophy.
13. The pharmaceutical composition of claim 11, wherein the disease due to the collapse of skeletal muscle is amyotrophy.
- 10 14. A pharmaceutical composition for treating ischemic disease, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 15 15. The pharmaceutical composition of claim 14, wherein the ischemic disease is cardiac infarction.
16. The pharmaceutical composition of claim 14, wherein the ischemic disease is stroke.
17. A pharmaceutical composition for treating conscious disturbance or motor disturbance caused by brain trauma, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 20 18. A pharmaceutical composition for treating a disease caused by demyelination of neurocyte, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 25 19. The pharmaceutical composition of claim 18, wherein the disease caused by demyelination of neurocyte is multiple sclerosis.
20. The pharmaceutical composition of claim 18, wherein the disease caused by demyelination of neurocyte is neuropathy of peripheral nerve.
- 30 21. A pharmaceutical composition for treating cataract, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 35 22. A pharmaceutical composition for treating inflammation, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
23. A pharmaceutical composition for treating allergic disease, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 40 24. A pharmaceutical composition for treating hepatic disease, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
25. The pharmaceutical composition of claim 24, wherein said hepatic disease is fulminant hepatitis.
- 45 26. A pharmaceutical composition for treating osteoporosis, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
27. A pharmaceutical composition for treating hypercalcemia, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 50 28. A pharmaceutical composition for treating a disease caused by abnormal activation of sex hormone receptors, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
- 55 29. The pharmaceutical composition of claim 28, wherein said disease caused by abnormal activation of sex hormone receptors is breast carcinoma.

30. The pharmaceutical composition of claim 28, wherein said disease caused by abnormal activation of sex hormone receptors is prostatic carcinoma.
31. The pharmaceutical composition of claim 28, wherein said disease caused by abnormal activation of sex hormone receptors is prostatomegaly.
32. A pharmaceutical composition for inhibiting the growth of tumor cells or for preventing metastasis of tumor, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
33. A pharmaceutical composition for inhibiting platelet-aggregation, which comprises, as an active ingredient, a compound of claim 1 together with pharmaceutically acceptable carriers.
34. A process for producing a cyclopropenone derivative of general formula (I):

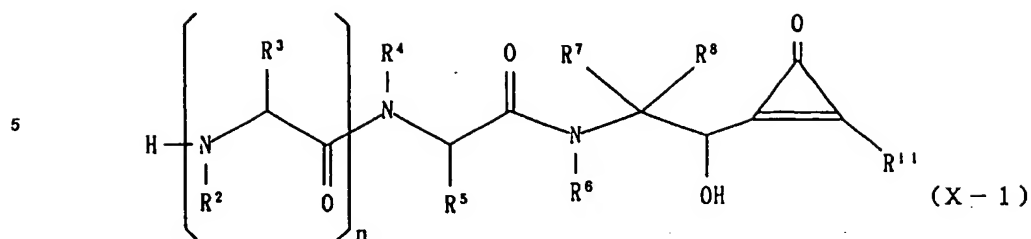


wherein R^1 is hydrogen atom, R^{12} -CO-, R^{12} -O-CO-, R^{12} -NH-CO- or R^{12} -SO₂- (in which R^{12} is C₁-C₂₀ alkyl group optionally substituted by one or more substituents selected from the group consisting of C₃-C₁₅ cycloalkyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₃-C₁₅ cycloalkyloxy group, optionally substituted C₆-C₁₄ aryloxy group, optionally substituted C₆-C₁₄ arylthio group, optionally substituted C₆-C₁₄ arylsulfonyl group, optionally substituted C₇-C₂₀ aralkyloxy group, optionally substituted heterocyclic group, oxo group, hydroxyl group, C₁-C₁₀ alkoxy carbonyl group and carboxyl group; C₃-C₁₅ cycloalkyl group; optionally substituted C₆-C₁₄ aryl group or optionally substituted heterocyclic group); R^2 , R^4 and R^6 each is independently hydrogen atom or C₁-C₁₀ alkyl group optionally substituted by C₁-C₅ alkoxy group or by C₁-C₅ alkylthio group; R^3 , R^5 and R^7 each is independently hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₀ cycloalkyl group, C₃-C₁₀ cycloalkyl group or optionally substituted C₇-C₂₀ aralkyl group; R^8 is hydrogen atom or C₁-C₂₀ alkyl group; R^7 and R^8 taken together may form C₃-C₁₅ cycloalkyl group; R^9 is hydroxy group or C₂-C₁₀ acyloxy group; R^{10} is hydrogen atom; or R^9 and R^{10} taken together may form oxo group; R^{11} is hydrogen atom, C₁-C₂₀ alkyl group optionally substituted by C₃-C₁₅ cycloalkyl group, C₃-C₁₅ cycloalkyl group, C₂-C₂₀ alkenyl group, optionally substituted C₆-C₁₄ aryl group, optionally substituted C₇-C₂₀ aralkyl group, optionally substituted heterocyclic group or -C(R^{13})(R^{14})-OH (in which R^{13} and R^{14} each is independently hydrogen atom, C₁-C₂₀ alkyl group, optionally substituted C₇-C₂₀ aralkyl group or optionally substituted C₆-C₁₄ aryl group, or R^{13} and R^{14} taken together may form C₃-C₁₅ cycloalkyl group); and n is 0 or 1 or a pharmaceutically acceptable salt thereof, which comprises:

(1) neutralizing a compound of formula (IX-1):

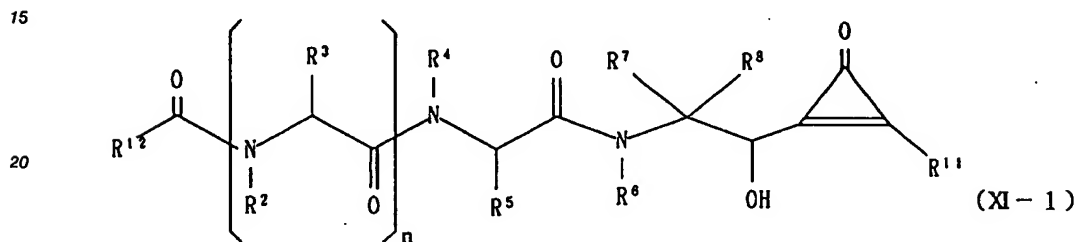


wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} , and n are as defined above and H-A is an acid by an alkali or an anion exchange resin to yield a compound of formula (X-1):



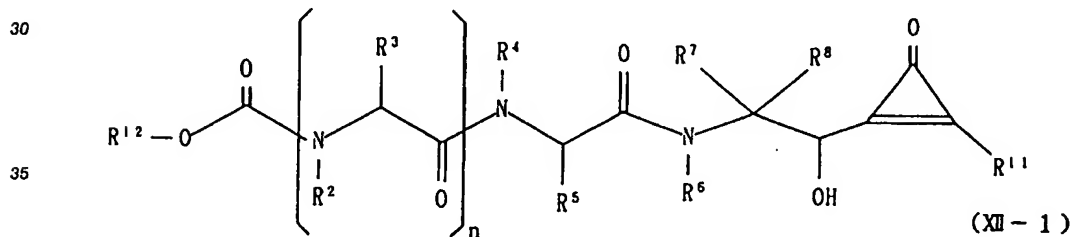
10 wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} , and n are as defined above;

(2) reacting the compound (IX-1) with an acyl chloride of formula $R^{12}\text{-CO-Cl}$ wherein R^{12} is as defined above to yield a compound of formula (XI-1):



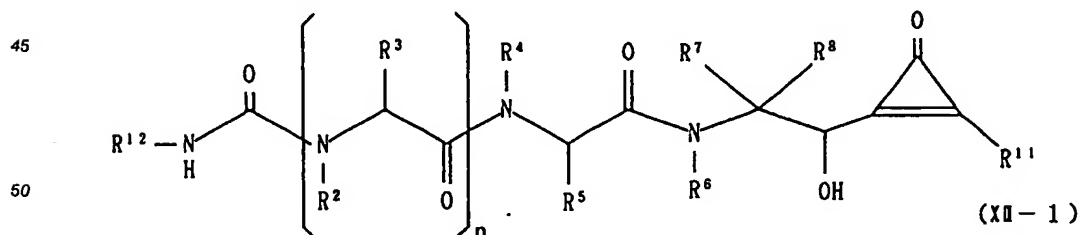
25 wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} , and n are as defined above;

(3) reacting the compound (IX-1) with a chloroformic acid derivative of formula $R^{12}\text{-O-COCl}$ wherein R^{12} is as defined above to yield a compound of formula (XII-1):



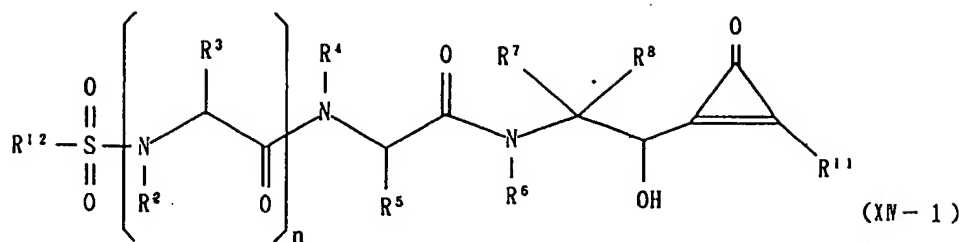
40 wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} , R^{12} , and n are as defined above;

(4) reacting the compound (IX-1) with an isocyanate of formula $R^{12}\text{-NCO}$ wherein R^{12} is as defined above to yield a compound of formula (XIII-1):

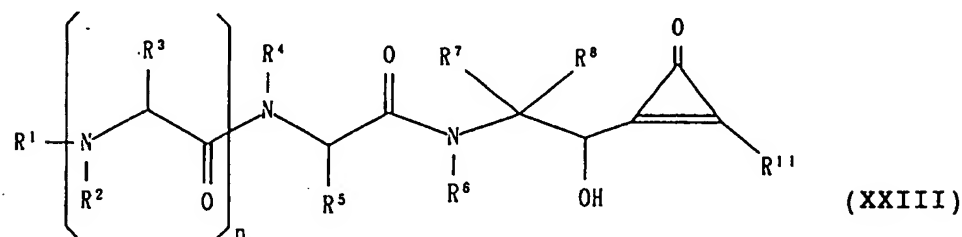


55 wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} , R^{12} and n are as defined above;

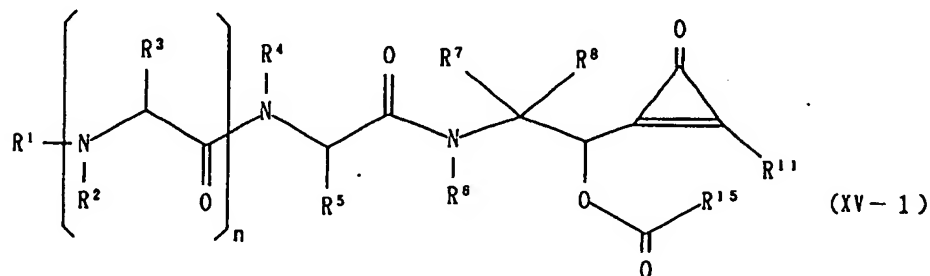
(5) reacting the compound (IX-1) with a sulfonyl chloride of formula $R^{12}\text{-SO}_2\text{Cl}$ wherein R^{12} is as defined above to yield a compound of formula (XIV-1):



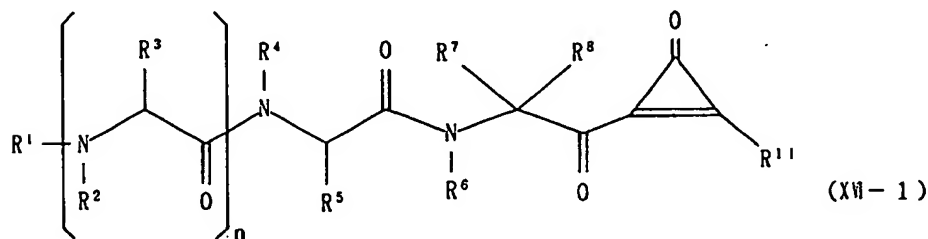
wherein $\text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^{11}, \text{R}^{12}$ and n are as defined above;
 (6) reacting a compound of formula (XXIII):



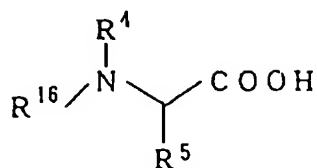
wherein $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^{11}$, and n are as defined above with an acyl chloride of formula R^{15}COCl wherein R^{15} is C_1 - C_3 alkyl to yield a compound of formula (XV-1):



wherein $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^{11}, \text{R}^{15}$ and n are as defined above;
 (7) treating the compound (XXIII) with an oxidizing agent to yield a compound of formula (XVI-1):

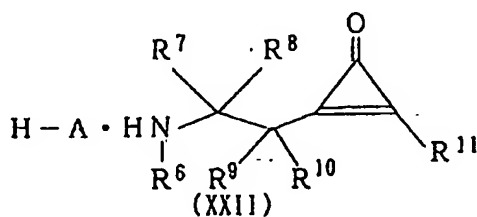


wherein $\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6, \text{R}^7, \text{R}^8, \text{R}^{11}$ and n are as defined above;
 (8) reacting a N-substituted amino acid derivative of formula (XVII):



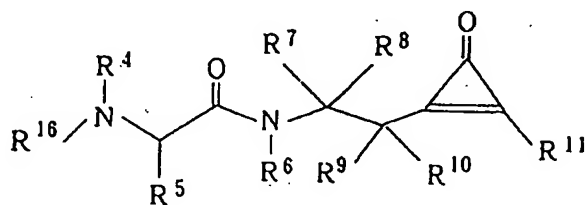
(XVI)

wherein R^4 , R^5 are as defined above and R^{16} is a group selected from a group consisting of R^{12} -CO-, R^{12} -O-CO-, R^{12} -NH-CO- R^{12} -SO₂- wherein R^{12} is as defined above in the presence of a condensing agent with a compound of formula (XXII):



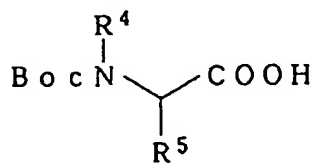
(XXII)

wherein H-A, R^6 , R^7 , R^8 , R^9 , R^{10} and R^{11} are as defined above to yield a compound of formula (XVIII):



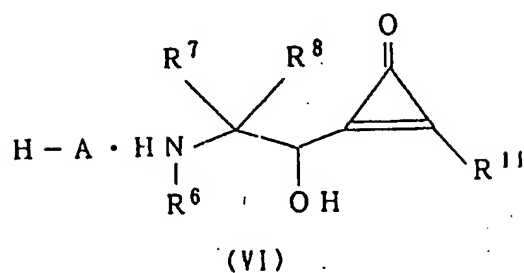
(XVIII)

wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , R^{11} and R^{16} are as defined above; (9) reacting a N-protected amino acid of formula (VII)

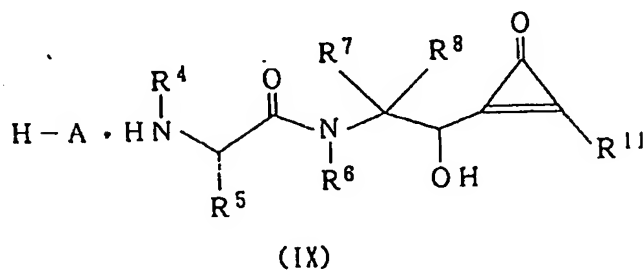


(VII)

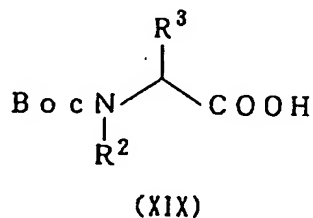
wherein R^4 and R^5 are as defined above and Boc is tert-butoxycarbonyl group in the presence of a condensing agent with a compound of formula (VI):



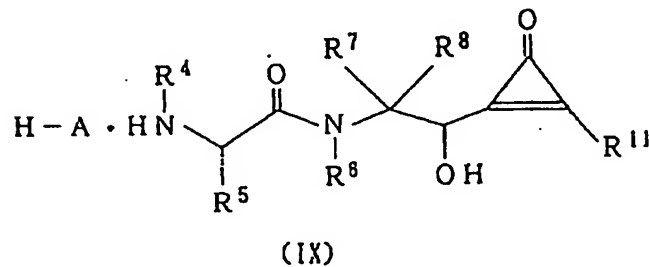
wherein R^6 , R^7 , R^8 , R^{11} and H-A are as defined above, and then with an acid to yield a compound of formula (IX):



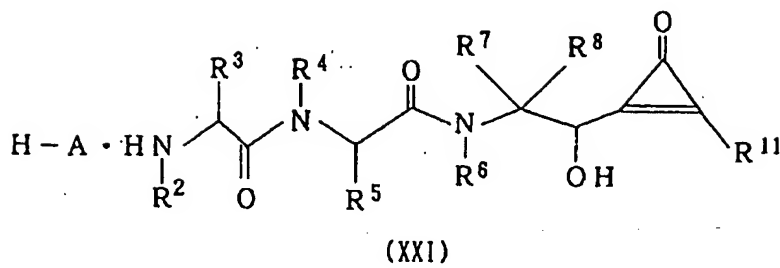
wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} and H-A are as defined above; or
(10) reacting a N-protected amino acid of formula (XIX):



wherein R^2 , R^3 and Boc are as defined above in the presence of a condensing agent with a compound of formula (IX):



wherein R^4 , R^5 , R^6 , R^7 , R^8 , R^{11} and H-A are as defined above, and then with an acid to yield a compound of formula (XXI):



wherein R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R¹¹ and H-A are as defined above.

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EUROPEAN SEARCH REPORT

Application Number

EP 92 11 0674

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. CL.5)
A	EP-A-0 393 457 (SUNTORY LIMITED) * pages 2, 24-30 ; claims 1-7 * ---	1,10-21	C07C271/18 C07C237/22 C07C333/04
A	EP-A-0 272 671 (SYNTEX INC.) * page 31 - page 32; claims 1-11,39-43 * ---	1,10-20	C07C317/24 C07C275/24 C07C311/03
A	EP-A-0 410 411 (MERREL DOW PHARMACEUTICALS INC.) * page 1 - page 15; claims 1,46-49 * ---	1,10-16	C07C311/29 A61K37/64 C07C237/04
A	GB-A-2 227 411 (SANDOZ LTD) * the whole document * ---	1,10-16	C07K5/06 C07C311/16 C07D211/62
A	EP-A-0 196 189 (TOYO JOZO KABUSHIKI KAISHA) * page 1 - page 3; claim 1 * ---	1,10-14	C07D307/68 C07D231/14 C07D213/81
A,D	JOURNAL OF ENZYME INHIBITION vol. 3, 1990, UK pages 195 - 201; TAKASHI SASAKI ET AL.: 'inhibitory effect of di- and tripeptidyl aldehydes on calpains and cathepsins' * page 198 - page 201 * ---	1,10	
A,D	TETRAHEDRON LETTERS. vol. 32, no. 10, 4 March 1991, OXFORD GB pages 1339 - 1342; MASAHIKO ISAKA ET AL.: 'one-pot synthesis of substituted cyclopropanone ketals via alkylation of 3,3-dialkoxy-2-sidocyclopropenes' * pages 1339,1341 * -----	1,34	
The present search report has been drawn up for all claims			
Place of search BERLIN		Date of completion of the search 24 SEPTEMBER 1992	Examiner RUFET J.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ***** & : member of the same patent family, corresponding document	